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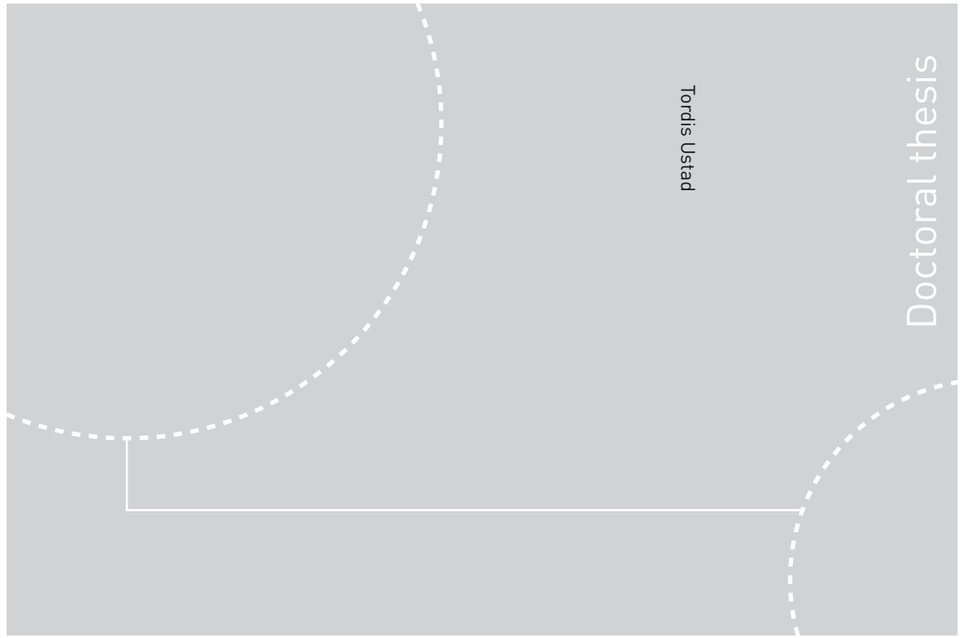

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Tordis Ustad

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

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Norges teknisk-naturvitenskapelige universitet
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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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Veiledere: Kari Anne Indredavik Evensen, Jorunn Helbostad, Lone Jørgensen
Finansieringskilde: ExtraStiftelsen Helse og Rehabilitering og Prematurforeningen samt forsknings midler fra St.Olavs Hospital, fra Unimed Innovasjons Forskningsfond og fra Klinikk for Kliniske Servicefunksjoner, St.Olavs Hospital.

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**.**

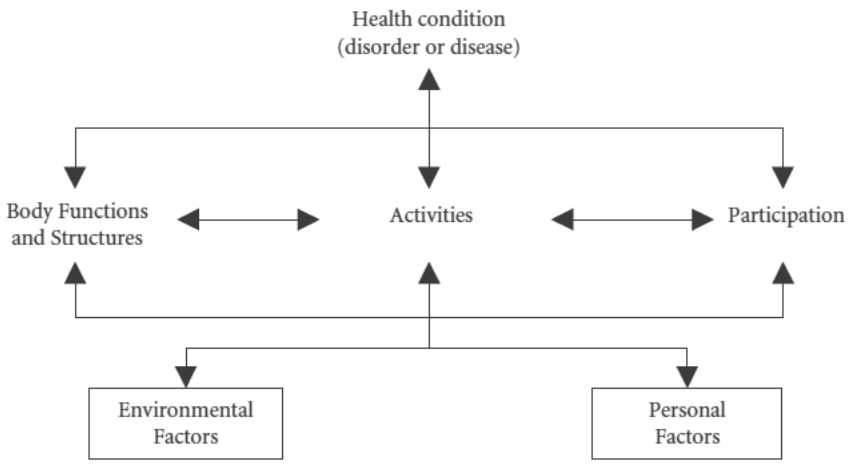

Figure 2. International classification of functioning, disability and health.[12]

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.

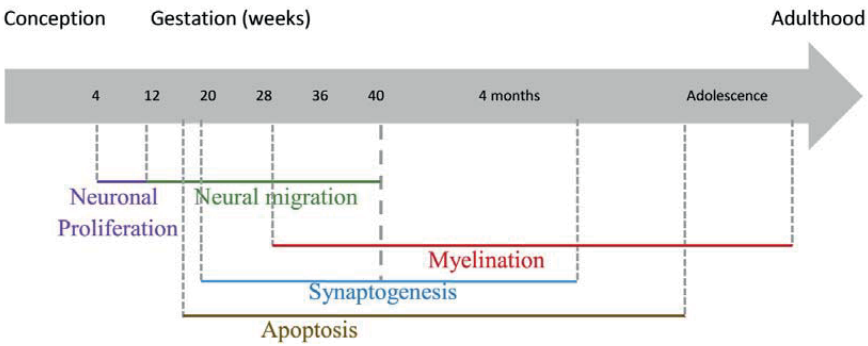

Figure 1. Timeline of major events in CNS development, adapted from Tau & Peterson.[23]

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).

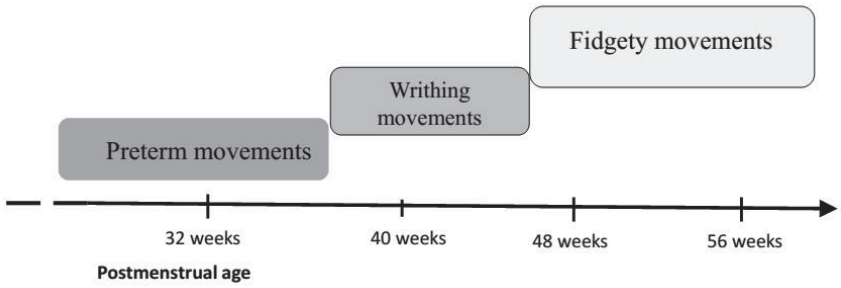

Figure 3. Age specific characteristics of general movements

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.

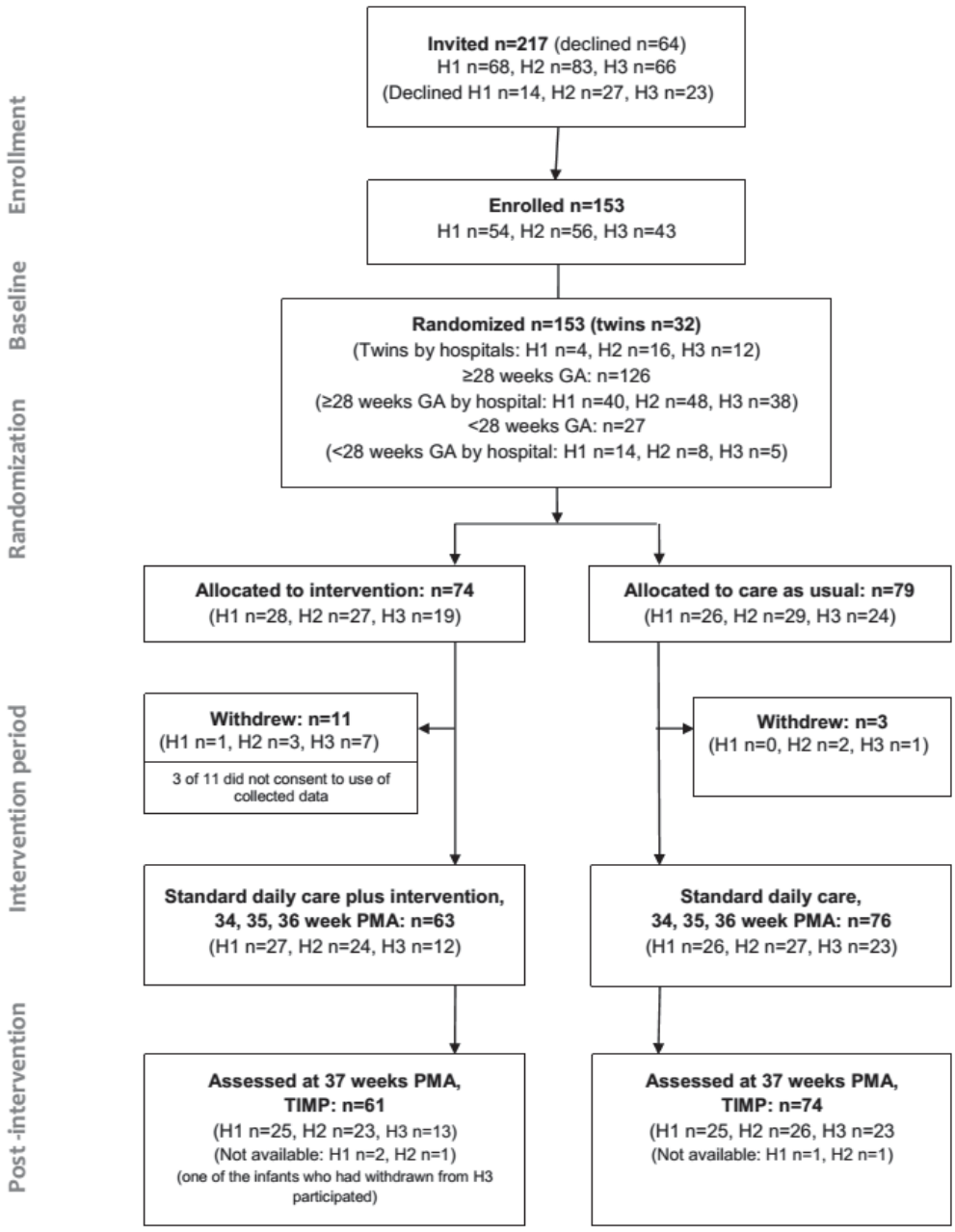

Figure 4. Participant flowchart from invited through randomisation, participation in intervention, and post-intervention assessment. H1: University hospital of North Norway, Tromsø University Hospital, H2: St. Olavs Hospital, Trondheim University Hospital, H3: Oslo University Hospital, Ullevål, PMA: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

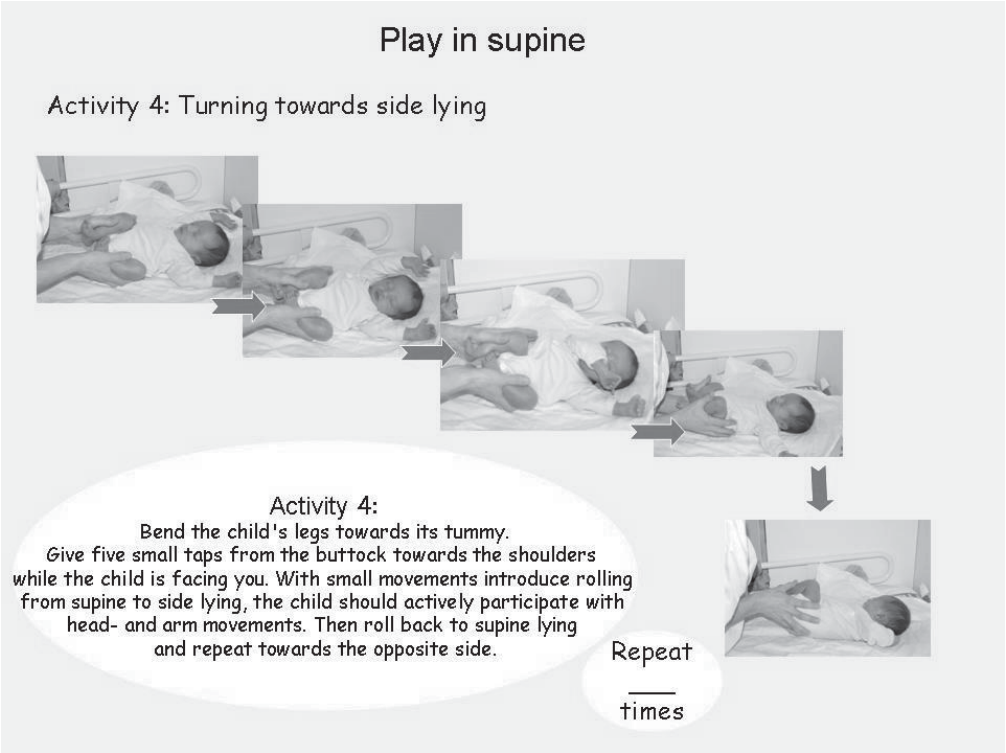

Figure 5. Page from the booklet given to the parents in the intervention group.

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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Appendix I

Randomized controlled studies of early intervention to optimize motor development and parent-infant relationship in infant born preterm the first three years of life.

Author	N	Inclusion criteria	Intervention	Country or City	Time of intervention	Outcome measure	Results
Focus on motor development							
Als et al. 2004[88]	33	GA between 28.4 – 33.3 weeks.	NIDCAP	US	From birth to discharge from hospital	At 2 weeks CA: APIB and neurological examination At 9 months CA: BSID-II	Significant differences favouring the experimental group at 2 weeks and 9 months CA in motor system, self-regulation, posture, state, BSID-II, mental and motor scale.
Blauw-Hospers et al.[137]	46	Abnormal GMs at 10 weeks CA	COPCA	Netherlands	From 3 – 6 months CA.	At 6 and 18 months: PEDI, BSID-II, AIMS and neurological examination.	There were no differences between the groups on any of the outcome measures.
Cameron et al 2005[126]	72	GA <32 weeks BW <1500g	Developmental PT weekdays from birth until discharge, there-after on a needs- and problem-orientated basis (parents education).	UK	Preterm age until 4 moths CA	At 4 months CA: AIMS	Intervention no significant effect on motor function. Subjects with high levels of parental compliance had higher scores on AIMS than those with lower parental compliance (p= 0.05).
Girolami 1994[111]	33	GA <35 weeks BW <1800g	NDT 14 – 28 sessions during 7 – 17 days	US	From 34/35 weeks CA lasting 7 – 17 days	NBAS Supplemental Motor Test	The intervention group scored significantly better than controls.
Hielkema et al 2011[134]	46	Abnormal GMs at 10 weeks CA	COPCA	Netherlands	From 3 and 6 months CA	At 3,4,5,6, and 18 months CA: IMP, neurological examination	No differences between the groups

Author	N	Inclusion criteria	Intervention	Country or City	Time of intervention	Outcome measure	Results
Lekskulchai 2001[101]	84	GA <37 weeks	Parent–administrated intervention to facilitate motor development.	Thailand	From 40 weeks – 4 months CA	TIMP	The intervention group showed significantly greater improvement in motor function compared to controls.
Morgan et al 20016[135]	30	Absent of fidgety at 3 – 4 months CA or likely CP diagnosis at 5-6 months.	GAME (goals, activity and motor enrichment)	Australia	From enrolment – 12 months CA	PDMS-2 COPM BSITD-III GMFM-66 and assessment of home environment and of parents' mental health.	Significant between group differences on the PDMS-2 in favour of GAME on the total motor quotient (B = 8.29, 95% CI 0.13-16.45, $p = 0.05$). Significant between group differences favoured GAME at 12 months on the cognitive scale of the BSITD-III and satisfaction scores on COPM.
Focus on both infant motor and cognitive development							
Bao et al. 1999[138]	156	GA 28 – 36.9 weeks.	Parents administrated intervention including motor, cognitive, speech development and social behaviour.	China	Term – 2 years	At 18 and 24 months; BSID-I	At 2 years, intervention group scored higher than the normal control ($p < 0.05$). Compared to normal control at 1.5 and at 2 years, the conventional care group scored significant lower in MDI.
Wu et al 2014[139]	211	GA <37 weeks BW <1500 g	Clinic-based intervention (CBIP), home-based intervention (HBIP) or usual care	Taiwan	From 7 days after birth – 12 months	At 12 months; Assessment of emotional regulation and observation of dyadic interaction. At 24 months; BSITD-III and the Child Behaviour Checklist	The CBIP-group: higher cognitive scores and lower rate of motor delay but attenuated when maternal or dyadic interactive behaviour was considered. The HBIP-group at 24 months: lower sleep problem scores and rate of internalizing problems and attenuated when duration of orientation to a toy or object was considered.

Author	N	Inclusion criteria	Intervention	Country or City	Time of intervention	Outcome measure	Results
Focus both on infant motor / cognitive development and parent-infant relationship							
Johnson et al 2009[140]	232	GA <32 weeks	Parent Baby Interaction Program (PBIP)	UK	In NICU – 6 weeks after discharge	BSID-II	No effect on maternal- stress No difference between the groups in MDI and the PDI scores
Kaaresen et al 2006/ 2008[90, 92]	146	BW <2000g	MITP: Seven 1–hour daily sessions last week before discharge and 4 sessions next 3 months	Norway	1 week before discharge – 3 months	2 years CA: BSID-II Parenting Stress Index (PSI)	BSID-II: No differences between groups, mental and motor scale. Maternal stress: significant lower
Koldewijn et al 2009[9, 141]	176	GA <32 weeks / BW <1500 g	IBAIP (home visit 1 hour x 6 – 8) / standard care	Netherlands		BSID-II, IBA and neurological examination	The intervention group performed better on BSID-II (MDI, p=0.02, PDI, p=0.008).
Kyno et al 2012[142]	118	GA 30 – 36 weeks	MITP, seven sessions last week before discharge and four sessions the next three months	Norway	1 week before discharge – 3 months	Ages & Stages Questionnaire: Social-Emotional, Child Behaviour Checklist, Mullen Scale of Early Learning.	No significant difference on cognitive, motor or behavioural development between the groups at 36 months CA
Oghi et al 2004[143]	23	PVL or IVH BW <2500 g	NBAS-based intervention by infant specialist. Second part; advice to mothers in handling	Japan	In the NICU – 6 months CA	BSID	The intervention group scored higher than the control group (n.s) Mean difference (95% CI): MDI: 8.5 (– 0.8, 17.8), PDI: 6.7 (– 1.9, 15.4).
Spittle et al 2009[144, 145]	120	GA <30 weeks	Infant development and parent-infant relationship	US	Term to 12 months CA	At 12 months CA; AIMS and NSMDA At 24 months CA; BSITD-III and parental questionnaires.	No significant differences between the groups in cognitive, language, or motor scores. The intervention group compared to controls; less externalizing and dysregulation behaviours and increased competence. Caregivers in the intervention group; less anxiety and depression.

Author	N	Inclusion criteria	Intervention	Country or City	Time of intervention	Outcome measure	Results
Teti et al[146]	173	African American and GA <37 weeks BW <2500 g	Psychoeducational components and parent-administered tactile stimulation component	US	From 32 – 36 weeks' PMA lasting 20 weeks	At 4 months; BSITD-II	No intervention effects were found for infant Bayley MDI or PDI scores or any infant anthropometric index at 3 – 4 months CA, nor were any main effects of intervention found on maternal sensitivity.
Focus on parent							
Ravn et al 2011[104]	93	GA 30 – 36 weeks	MITP, seven sessions last week before discharge followed by four sessions the next three months	Hospital in Norway	1 week before discharge – 3 months	Video-observation of mothers	Mothers in the intervention group scored significantly higher on sensitivity / responsiveness compared to controls.
White-Traut et al 2013[105]	198	GA 29 – 32 weeks or 2 social-environmental risk factors in mothers	Auditory, tactile, visual, vestibular stimulation	US	32 w PMA – 6 weeks CA	Mother- infant interaction during feeding and play	Intervention dyads higher odds of high versus low responsivity compared to control dyads.

AIMS: Alberta Infant Motor Scale[47], APIB: The Assessment of Preterm Infants' Behavior[104], BSID-I/II: Bayley Scale of Infant Development, BSITD-III: Bayley Scale of Infant and Toddler Development[48], COPCA: COPing with and CAring for Infants with Special Needs[148], COPM: Canadian Occupational Performance Measure[149], GMFM-66: Gross Motor Function Measure 66[150], IBA: Infant Behavioral Assessment[142], IMP: Infant Motor Profile[49], MITP: Mother- infant transaction program[134], NBAS: Neonatal Behavioral Assessment Scale[151], NDT: Neurodevelopmental treatment[152], NIDCAP: Newborn Individualized Development Care and Assessment Program[87], PEDI: Pediatric Evaluation of Disability Inventory[153], PDMS-2: Peabody Developmental Motor Scales 2[52], NSMDA: Neurological Sensory Motor Development Scale[51], SPEDDI: Supporting Play Exploration and Early Development Intervention[128], d

Appendix II

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BMC Pediatrics

STUDY PROTOCOL Open Access

Study protocol: an early intervention program to improve motor outcome in preterm infants: a randomized controlled trial and a qualitative study of physiotherapy performance and parental experiences

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Abstract

Background: Knowledge about early physiotherapy to preterm infants is sparse, given the risk of delayed motor development and cerebral palsy.

Methods/Design: A pragmatic randomized controlled study has been designed to assess the effect of a preventative physiotherapy program carried out in the neonatal intensive care unit. Moreover, a qualitative study is carried out to assess the physiotherapy performance and parents' experiences with the intervention. The aim of the physiotherapy program is to improve motor development i.e. postural control and selective movements in these infants. 150 infants will be included and randomized to either intervention or standard follow-up. The infants in the intervention group will be given specific stimulation to facilitate movements based on the individual infant's development, behavior and needs. The physiotherapist teaches the parents how to do the intervention and the parents receive a booklet with photos and descriptions of the intervention. Intervention is carried out twice a day for three weeks (week 34, 35, 36 postmenstrual age). Standardized tests are carried out at baseline, term age and at three, six, 12 and 24 months corrected age. In addition eight triads (infant, parent and physiotherapist) are observed and videotaped in four clinical encounters each to assess the process of physiotherapy performance. The parents are also interviewed on their experiences with the intervention and how it influences on the parent-child relationship. Eight parents from the follow up group are interviewed about their experience. The interviews are performed according to the same schedule as the standardized measurements. Primary outcome is at two years corrected age.

Discussion: The paper presents the protocol for a randomized controlled trial designed to study the effect of physiotherapy to preterm infants at neonatal intensive care units. It also studies physiotherapy performance and the parent's experiences with the intervention.

Trial registration

ClinicalTrials.gov NCT01089296

Keywords: Preterm infants, early intervention, Physiotherapy, Motor development, Parental experience

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Background

Preterm children are at increased risk of motor impairments and these impairments often persist into adolescence [1]. Evidence regarding the effect of physiotherapy to improve motor development in preterm infants is limited [2]. Interventions designed for promoting development in these infants have been heterogeneous and studies reporting a significant impact of early intervention on motor development are sparse [2,3]. Examining an approach in which the therapy is adapted to the individual premature infant's needs may contribute to knowledge about how to enhance motor development in these infants. To that end we designed a study on the effects of physiotherapy in infants born prematurely as well as on professional performance and parents experiences. The intervention is performed before the infant's reach term age.

The study, named "The Norwegian Physiotherapy Study in Preterm Infants" (NOPPI), consists of a pragmatic randomized controlled trial and a qualitative observational and interview study. The project provides a new approach to intensive physiotherapy consisting of several more elements than today's traditional approach. The intervention integrates key elements from the modified version of the Mother-Infant Transaction Program performed in a study by Kaaresen and colleagues [4,5], as well as elements from interventions in other studies which have shown a positive effect on premature children's motor development [2,3,6-9]. NOPPI explores the effects of individually customized physiotherapy on preterm infants before they reach term age as well as assess the physiotherapy performance and parental experiences of participating in carrying out the intervention in the neonatal intensive care unit (NICU). Outcomes are measured up to two years of age.

The theoretical framework related to the physiotherapy intervention in this study is knowledge of newborn behaviors [10,11], the importance of parental competency [5,12] and theories of motor development, including neuroscience and phenomenology of the body [13-15]. A brief presentation of the framework follows.

Newborn behaviour and parental competency

Competency in behavioral organization makes active social participation possible for infants [10,11]. As a group, however, prematurely born infants with very low birth weight, and particularly those with serious complications, are reported to have more difficulties in behavioral regulation than infants born at term [16,17]. This may be expressed by the infant as irritability, requiring a long time to settle into a routine and fluctuating attention. Infants' neurobehavioral functioning unfolds through maturation and experience, and the individual can be helped to self-regulate by the caregiver and environmental adaptations. Parental competency to read and understand the individuality and needs of their infant is significant in decreasing parental stress [5] and enhances cognitive outcome and social functioning in the infants [18].

Phenomenology of the body

The body forms the base from which both the infant as a person and the world are constituted. A newborn's body is a tactile-kinesthetic body. Through moving, infants learn and experience movements by which kinesthetic competency develops [19,20]. On the basis of innate spontaneous movements, the infant learns to know their own body as well as gaining knowledge and realization of the surroundings. Their bodies are both expressive and experienced at the same time. Thus, child development can be understood as a result of interaction among the system consisting of perception, sensation and movement.

Theory of motor development

The motor development of a child is non-linear [21,22] and regarded as a product of both genetic processes and experiences [23,24]. In dynamic systems theory [25], motor development is believed to be a feedback process based on interaction among different subsystems in the child, the environment and the task. There is a shift from trial and error phases of instability to stable movement in which the synergy of appropriate movements is used to perform a functional task [23]. The motor patterns of healthy children appear flexible, adaptable and dynamic [23].

The motor patterns of preterm infants are dominated by extension and to a lesser degree flexion when compared to infants born at term [26]. This fact, in addition to possible brain damage, may influence the children's spontaneous motor experiences and the process of developing stable motor strategies as they grow. Motor function is related to the development of postural control which is necessary to transfer and modify body weight distribution for appropriate functional movement, communication and social interaction [27,28]. To have postural control is then about maintaining a bodily position over time, regaining postural stability after perturbations, managing changes between different postures, and integration of postures into locomotion and exploration [27]. Interventions that optimize postural control and selective movement in preterm infants may therefore be important in reducing the degree of delayed motor development or the severity of cerebral palsy (CP).

The human brain in infancy is highly plastic and there is an active growth of dendrites and formation of

synapses. Experience influences and models the brain and leads to structural changes [24,29] in, e.g., the number of synapses that are developed, the synapses' position and functioning, as well as elimination of synapses that are not needed. Motor skills may be highly influenced by early intervention because the motor pathways forming the corticospinal tracts already show mature myelin at term age [30] and myelination may be activity-dependent [31].

There is some evidence that recovery from central nervous system injury in infants can be understood both by new growth of motor neurons and creation of new synapses. Moreover that part of the brain is not yet developed for specific tasks and may be developed for other uses than were originally intended [24]. Of these insights about brain plasticity it is suggested that early-targeted customized individual intervention could be of great importance to the development of movement quality and function of preterm children.

Methods/Design

NOPPI consists of two related parts. The aim of the first part, the pragmatic randomized controlled trial, is to evaluate the effect of customized physiotherapy on preterm infants' motor development when the intervention is performed by the parents during a period of three weeks while the infant resides in the NICU. The endpoint is motor development at 24 months of corrected age (CA).

The aim of the second part, the qualitative observation and interview study, is one: to analyze and identify aspects of physiotherapy performance important for teaching parents practical knowledge, and two: to increase our knowledge about parents' experiences of active involvement in implementation of the intervention designed to promote their child's motor development, as well as the short and long term effects on the parent-child relationship. The endpoint is 24 months CA.

The study is approved by the Ethic Committee of Northern Norway (REK nord: 2009/916-7).

Part one

Study sample

Prematurely born infants at the University Hospital Northern Norway HF, Tromsø, Norway, and University Hospital Trondheim HF, St. Olavs Hospital, Norway, with gestational age (GA) at birth ≤ 32 weeks are eligible for the study. The infants must be able to tolerate handling at postmenstrual age (PMA) week 34 and their parents have to understand/speak Norwegian. In addition it is required that the follow-up program takes place at the respective hospitals outpatient clinics. Exclusion criteria are triplets or higher plurality, major malformations or recent surgery.

Sample size calculations

Power calculation was performed. Our outcome measure at 24 months CA is the Peabody Developmental Motor Scales-2 (PDMS-2) [32]. We consider a difference on gross motor and fine motor function measured on PDMS-2 between the intervention and the control group of 0.5 SD as clinically significant. As a result there must be 63 children in each group to have an 80% chance to detect a 0.5 SD difference between the groups with a significance level of 0.05 (alpha) on two-sided tests. When we consider potential attrition and the effect of including twins, we aim to recruit 150 children, i.e., 75 in each group for part one of the study.

Recruitment procedure

Enrollment of participants is a process taking place at the neonatal units of two Norwegian University Hospitals. Oral and written information is given to parents of the preterm babies fulfilling the inclusion criteria. Professionals not involved in the daily care and treatment of the child when the child is 33 weeks PMA conduct the interview. It is the project leader who performs the recruitment interview in Tromsø, while the representative in the project leader group in the other Hospital (St. Olavs Hospital, Trondheim) addresses the parents in Trondheim. Informed consent forms signed by the parents are delivered to a nurse or physiotherapist in the neonatal unit if the parents agree to participate, after which the baseline assessment is performed.

Randomization process

The infants are randomly assigned either to the intervention or to the control group. Randomization is performed by a web-based randomization system developed and administered by the Unit of Applied Clinical Research, Institute of Cancer Research and Molecular Medicine, Norwegian University of Science and Technology, Trondheim, Norway. Stratification is according to GA at birth (< 28 week and ≥ 28 weeks) and recruitment site. In the case of twins both children are randomized to the same group because of the nature of the intervention. The randomization takes place *after* the assessment of baseline motor performance (Figure 1) so that the therapists will not be biased one way or the other by knowing the group assignment.

Intervention

Practitioners Experienced physiotherapists in pediatrics are implementing the intervention and perform the assessments. In each research centre two physiotherapists are dedicated to performing the baseline assessment and teaching the treatment protocol to the parents of the intervention group infants. Each therapist maintains records (log) over the number of clinical

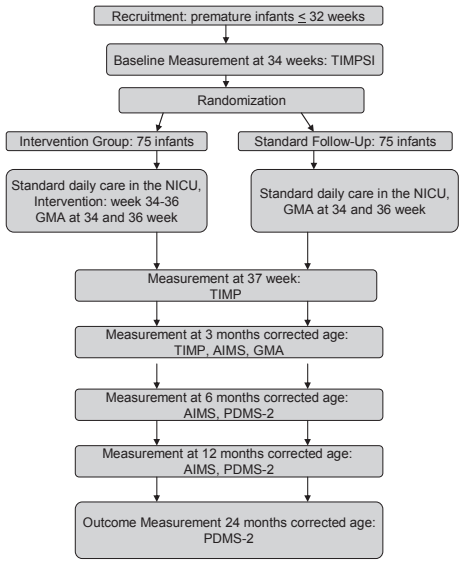

Figure 1 Flowchart of the quantitative study, part one.

consultations with the individual child and parent and notes what has been emphasized in the consultations. Two other physiotherapists blinded to group assignments perform the follow up assessments when the child is at term and at three, six, 12 and 24 months CA. The physiotherapists are assessed for rater reliability for the standardized tests used.

Content of intervention The intervention involves education of parents in individualized handling and motor stimulation of their child. The handling and motor stimulation program is primarily based on Girolami and Campbell [6], and the performance is integrated into communication and social interaction between the caregiver and the infant [5]. The parent at the bedside of the child during the NICU admission period is the one carrying out the daily intervention after being taught by the physiotherapist. The objective of the intervention in which the main elements are postural support and movement facilitation techniques, is on improving symmetry of posture, muscle balance, and movement in infants, all of which are supporting the foundation of the execution of functional activities in the infant's daily life. The facilitating technique is intermittent adjusted pressure/compression over relevant muscle groups and joints when the infant is in supine (Table 1), prone (Table 2), sidelying (Table 1) and in supported sitting (Table 2). There are also transition activities in which the infant is guided from supine to sidelying and from supine through sidelying to upright supported sitting (Table 1). The physiotherapist chooses appropriate exercises and modifies handling for each infant's level of development and tolerance for movement; the intervention always includes one or more activities in each position. A main goal is development of head and trunk control in each position.

Functional goals and activities for the child in supine include: maintaining head in midline, rotating the head to right and left, bringing hands to mouth and hands to chest, adjusting their own position, turning from supine to side (Table 1). Sidelying activities include maintaining a comfortable position with head flexed toward chest, bringing hands to mouth (Table 1). Prone activities include assisting the infant to lift and turn the head to the middle and to right and left sides, adjust their position, take weight on forearms, bring the hands to the mouth, look for the caregiver (Table 2). Finally, supported sitting activities include maintaining controlled upright and midline posture of the head with good trunk extension, being able to turn the head to track and using the arms for forward reaching (Table 2).

Intervention is carried out for up to ten minutes, twice a day, over a period of three weeks (PMA weeks 34, 35, 36). During intervention the infant should be in "State of arousal level" three (eyes open, no movements) or four (eyes open, large movements) according to Prechtl's states [33]. The length of each treatment session is adjusted depending on the infant's response and condition. Intervention is terminated if the infant shows any of the following signs which are interpreted as expressions of stress or discomfort: makes faces, changes skin color, has irregular respiration, undesired changes in muscle tone, uncontrolled movements or continual changes in the state of arousal level. Performance time is adjusted to the infant's daily rhythm. Intervention may be carried out half an hour before a meal, between two meals or any time when the child has a state of arousal level of three or four. Parents record the time of each intervention and the number of interventions each day. If necessary they note concisely why intervention was not completed. At the very beginning of the intervention period parents receive a "play book" in which they find pictures and written explanations of each "exercise" they will be performing during the intervention period. The parents have to demonstrate their ability to do the activities the second and the eighth day of the intervention.

Test instruments Demographic data as well as information about current diseases are collected from patient records, from the NICU's online registration program and by interviewing the parents. All infants participating in the study are assessed with standardized tests at term age, three, six, 12 and 24 months CA (Figure 1). Motor development at baseline is assessed using the Test of

Table 1 The protocol for promotion of postural and selective control of movements, supine and sidelying

Objectives	Performer activity	Activity goals for the child
1. Increase strength, balance. Control of the anterior and posterior neck muscles.	1. Activating neck flexors, shoulder and abdominal muscles through intermittent caudal compression.	1. Maintain head in midline and head turning to both sides.
2. Increase strength and control of the anterior shoulder and chest muscles and balance between anterior and posterior shoulder and chest muscles.	2. Horizontal intermittent pressure through the shoulders. Assist the child to bring arms forward to the mouth or on chest.	2. Bringing hands forward, hands to mouth and hands on chest.
3. Increase strength and control of the abdominal muscles.	3. Through lifted pelvis and flexed legs, provide intermittent compression toward shoulder.	3. Antigravity pelvis and lower extremity lifting with hip and knee flexion
4. Affect alignment, righting reactions and antigravity muscle activity in the trunk in the sagital and frontal planes.	4. From the lifted pelvis and control at shoulders, shift the infant's weight in small increments from side to side. When possible allow the infant to control the head and arms without assistance.	4. Rolling from supine to side.
5. Affect alignment, righting reactions and balance and control between the anterior and posterior neck and trunk muscles.	5. Guide the child from supine through sidelying to upright sitting.	5. Maintaining head control in midline during the transition with minimal assist.
6. Increase strength of the anterior neck muscles lateral head righting and neck and cervical extensors when rolling into prone.	6. Guiding upper shoulder slightly backwards with small weight shifting movements while supporting the child with one hand under head.	6. Keep the chin tucked during movements from supine to prone and when in sidelying
7. Increase the strength of the anterior chest and shoulder muscles.	7. Horizontal intermittent compression through the shoulders. Assist the infant in bringing the hands to mouth or toward the midline.	7. Bring hands to mouth or bring hands forward to chest.
8. Elongation of thorax and lumbar muscles; increase strength, balance and control of abdominal and trunk muscle groups.	8. Lifting pelvis laterally upward to lengthen the weight-bearing side of trunk and activate lateral muscles of the trunk and head on the non-weight-bearing side. Facilitate rolling from supine to side. Head, neck, trunk and pelvis are in alignment.	8. Maintain the pelvis in a neutral position while flexing the hip and knee. Improved antigravity strength of the lateral neck and trunk muscles

1-5: The child is in supine. 6-8: The child is sidelying

Table 2 The protocol for promotion of postural and selective control of movements, prone and sitting

Objectives	Performer activity	Activity goals for the child
1. Increase strength, balance and control in the anterior and posterior neck and upper back muscles.	1. Intermittent compression through shoulders in caudal direction is used to activate the neck muscles, pectoralis muscles and upper back extensors.	1. Lifting the head from the surface and turning the head to right and left side.
2. Increase strength and balance of the anterior and posterior shoulder muscles.	2. Mild intermittent horizontal compression through shoulders to activate the anterior and posterior shoulder and scapular muscles.	2. Bring the hands to mouth.
3. Downward rotation and stabilization of the scapula.	3. Small weight shifts to one side to facilitate head turning by providing compression down the non-weight-bearing side and elongation of the weight-bearing side.	3. Strength and control of shoulder girdle to provide a stable base for head lifting and turning.
4. Increase activity and strength of the abdominal muscles.	4. Support and tactile input over the abdominal muscles to increase activation in the sagital and frontal planes.	4. Maintain the pelvis in neutral to provide stable base of support for trunk extension and sagital and frontal plane weight shifts.
5. Increase strength and control of neck muscles; elongation of cervical spine.	5. Intermittent compression through the shoulders in a caudal direction to facilitate balanced activation of the anterior and posterior neck, chest and abdominal muscles.	5. Maintain the head up and in midline.
6. Increase strength, balance and control of anterior and posterior neck muscles and downward rotation of the scapula.	6. Intermittent horizontal compression through shoulders and chest muscles to assist the infant to bring the hands together in midline or to the mouth.	6. Maintenance of scapular depression to assist in bringing hands to midline.
7. Integrate control of abdominal muscles and back extension muscles; increase the strength of abdominal muscles; improve balance of trunk flexor/extensor muscle activity.	7. Support the head and shoulders and tip the infant approximately 15 degrees backward to activate neck and abdominal muscles. From this position add very small lateral movements to activate trunk in the frontal plan, elongating the weight-bearing side of the body to promote lateral righting of the head and trunk.	7. Maintain capital flexion, chin toward the chest with hips and knees in neutral flexed position.

1-4: The child is in prone. 5-7: The child is in sitting

Infant Motor Performance Screening Items (TIMPSI) at 34 weeks PMA. The TIMPSI addresses the main targets for the intervention, postural control and selective movements. The primary outcome measure is motor development at two years CA on the Peabody Developmental Motor Scales (PDMS-2). The PDMS-2 was chosen because the test assesses both fine and gross motor function, i.e., harmonizing with the intervention targets of postural control and selective movements. The PDMS-2 is also administered at six months and 12 months CA (Figure 1). Secondary outcome measures are: the General Movement Assessment (GMA) at 34 weeks, 36 weeks, and three months CA, the Test of Infant Motor Performance (TIMP) at 37 weeks, and three months CA, and the Alberta Infant Motor Scale (AIMS) at three months, six months, and 12 months CA (Figure 1).

Test of Infant Motor Performance Screening Items Scores on the Test of Infant Motor Performance Screening Items (TIMPSI) form the baseline for assessment of each infant's motor performance prior to initiation of the intervention. The TIMPSI assesses movement and postural control in prone, supine, and supported sitting and standing and takes approximately 20 minutes to administer [34]. The TIMPSI is composed of three subsets of items taken from the Test of Infant Motor Performance (see next paragraph). Prior to assignment to one of the TIMPSI subsets, TIMP items were psychometrically analyzed using Rash analysis. The first set of eleven items, representative of the full TIMP, is administered. Based on the infant's score, either an "easy set" (ten items) or a "hard set" (eight items) is administered [34]. The test results are used in the ultimate statistical analysis of results as well as to determine the emphasis of the treatment protocol.

The Test of Infant Motor Performance The Test of Infant Motor Performance (TIMP) identifies age-appropriate or delayed motor development in infants and shows changes in motor development with increasing age [34]. The test evaluates postural control-stability and alignment of parts of the body - in addition to the child's reactions to visual and auditory stimuli. The TIMP is valid for use from 34 weeks PMA until five months CA. The test consists of 13 Observed Items and 29 Elicited Items [34]. Previous studies have demonstrated that the TIMP is responsive to intervention in preterm infants both prior to term age [6] and from term to four months CA [35]. The age of testing is best at approximately the same time within normative windows for all children in the study, i.e., the test is performed as close to the middle of the two-week age window as possible.

Prechtl's Method of General Movement Assessment Prechtl's Method of General Movement Assessment (GMA) identifies normal and abnormal quality of movement (CP)[36]. The GMA is valid for use from preterm age until about five months CA. The scoring, based on taped observation of spontaneous movement recorded while the infant is supine, is considered to be a non-invasive assessment because no handling is involved. Recommendations for the recording technique [36] include video recordings from five to thirty minutes in duration depending on the age and activity level of the infant. General Movements are first clearly defined as either normal movement patterns or abnormal ones, following which abnormal General Movements are classified in different subgroups dependent of the infants age [36]. The subgroup at the age of 34 and 36 PMA are Poor Repertoire (PR), Cramped-Synchronized (CS) and Chaotic (CH) General Movements. At three months there is No Fidgety (F-) or Abnormal Fidgety Movements (AF). Both the TIMP and the GMA are used for concurrent assessment at term and three months CA because at term age they have been shown to predict different aspects of development at one year of age, i.e., TIMP scores are related to functional performance and the GMA to locomotion at one year [37]. The GMA has high sensitivity and specificity for the prediction of CP by three-four months CA [38,39].

Alberta Infant Motor Scale The Alberta Infant Motor Scale (AIMS) examines delayed and abnormal motor development in infants over time and is valid for assessment from term until 18 months of age [40]. The test, selected because of good psychometric properties, is quick to administer with limited handling and focuses on both achievement of motor milestones and quality of posture and movement outcomes [41]. The age of testing is done at approximately the same time within the one-month normative window for all children at three, six and 12 months CA, i.e., the test is performed as close to the middle of the age window as possible. Pin and colleagues [42] demonstrated the sensitivity of the AIMS items to differences in preterm infant motor development that typically result in lower scores for preterm than for full term infants [32].

Peabody Developmental Motor Scales The Peabody Developmental Motor Scales (PDMS-2) assesses both fine and gross motor function [32]. The test is valid from term through five years of age. PDMS-2 consists of six subtests e.g. Reflexes, Stationary, Locomotion, Object Manipulation, Grasping and Visual-Motor Integration. The results of the subtests may be used to generate three global indices of motor performance. These composites are Gross Motor Quotient, Fine Motor Quotient and Total Motor Quotient [32]. The three composites of the PDMS-2 exhibit high test-retest reliability and acceptable responsiveness to intervention effects

[43]. The test is suitable to use as a motor measure for children with CP at two years of age [43].

Data collection Both the intervention group and the control group receive standard medical and nursing care while hospitalized. The Newborn Individualized Development Care and Assessment Program (NIDCAP) [44,45] forms the principal approach in the NICU. In addition the intervention group receives the handling and facilitation program. The nurses are not blinded for the group assignment because it is impossible to prevent them from observing the parents providing the intervention protocol. However, we discussed prior to the initiation of the study the need to refrain from applying the intervention to any infants in the NICU.

After discharged from the hospitals, infants from both groups return for the follow up at the Hospitals' outpatient clinics. If the pediatrician and the physiotherapist assessing the infant judge additional physiotherapy to be needed after discharge, individuals will be referred to therapy independent of group assignment. The physiotherapist in the outpatient clinic records information if infants receive physiotherapy after discharge from the Hospital.

Analysis Demographic data will be collected and described with descriptive statistics. Group differences will be analyzed using linear mixed models for continuous data and generalized estimating equations (GEE) for categorical data. These methods make it possible to account for the possible clustering effect by including twin pairs and for repeated measurements. Z-scores will be used in the longitudinal analyses as different tests are used, as the child gets older. All the tests are double sided tests and p-value < 0,05 is considered significant. SPSS and Stata will be used in the analyses.

Data storage Test results are recorded on original test forms and stored safely. The results are entered into a secure research database at the University Hospital of Northern Norway using the statistical program SPSS.

Part two

Study sample

Part two involves a qualitative study based on a subset of subjects from the clinical trial: eight triads (physiotherapist, parent and infant) from the intervention group and parents of eight infants in the control group.

Recruitment procedure

Parents of infants from the intervention and from the control group are invited to participate in the qualitative study. Recruitment is an ongoing process until we have the planned number of sixteen participants.

Design

Part two of the study has an exploratory design [46]. Because the objective is both to increase knowledge about physiotherapy performance and to increase the understanding of parents' experience of being actively involved in implementation of the intervention, as well as the effects on the parent-child relationship in short and long term, repeated observation and qualitative interviews are chosen as the research methods. The schedule for observations and interviews is described in Figure 2.

The observations of clinical encounters with participants from the intervention group focus on what is going on in the situation, i.e., communication and interaction between the parent and therapist, between the therapist and infant and between the parent and infant during therapy. The clinical encounters are videotaped. In addition there are qualitative semi-structured interviews with the caregivers from both groups. The themes in the interview guide include: feelings and observations about the infant, interplay and interaction with the infant. For the intervention group the topics also include parents' guidance and parents' reflections on cooperation with the physiotherapist and the experience of the intervention. There are open-ended questions.

The intervention group • Observation and video recording of the TIMPSI in PMA week 34, parents present, the first two consultations after the TIMPSI and eight days after the last consultation in week 34.

• Interview with the parent who carries out the intervention: before discharge from hospital, and at follow up at three, six, 12 and 24 months CA. Interviews will be audio recorded.

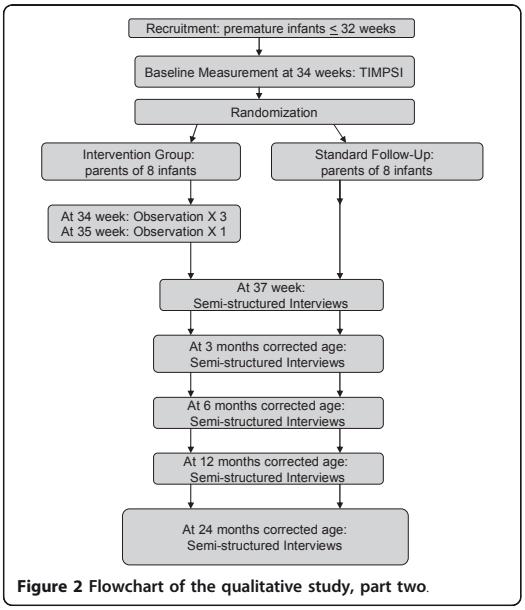

Figure 2 Flowchart of the qualitative study, part two.

The control group • Interview with the parent who spends most time at the hospital with the child during the neonatal admission period for the eight children in this group. Interviews will be recorded and carried out before discharge from hospital, and at three, six, 12 and 24 months CA.

Observational and interview personnel

The project leader and the collaborating partner who is a member of the project leader team in Trondheim are doing the observations and the interviews in, respectively, Tromsø and Trondheim. Neither of the researchers are therapists for the infants and parents participating in the qualitative part of the study. Both researchers are physiotherapists, have been working in the field of pediatrics for several years, and are skilled in observation and interview techniques.

Data analysis

A phenomenological-hermeneutic analysis ad modum Lindseth and Norberg [47] will be carried out on the data material from the observations and interviews. The interpretation process will follow the hermeneutic circle from whole to part and part to whole. Steps in the process of analysis:

1. Each video clip is studied and the general impression is summarized.
2. Structural analysis of each situation. Identification of main theme and sub theme.
3. Description of main theme and sub themes.
4. Structural analysis is compared with the general impression from the video clips.
5. Revision and adjustment by repeating 1-4.
6. All the video clips with main theme and sub themes are studied in the same context.
7. A complete interpretation of the data is produced.

The same process of analysis is used for the transcripts of the interviews. Trustworthiness (credibility and dependability of the findings) will be established through triangulation of the deriving themes of two or three researchers.

Discussion

This paper presents a health promoting individually customized physiotherapy program designed for preterm infants before they reach term age to improve the infants' motor development. The intervention program is based on current theoretical frameworks and includes aspects of previously successful interventions such as the significance of infants' behavioral regulation and parent competency in social interaction. The design is appropriate for implementation in a NICU setting, but may be feasible to pursue in a community setting and generalized across different groups of high risk infants. The Norwegian Physiotherapy Study in Preterm Infants provides an opportunity to determine whether an individually customized three-week physiotherapy program for preterm infants in the NICU, will enhance the infants' motor development at two years CA. The study will also provide insight into the process of communicating practical knowledge to parents and the value of parent's handling competency in interaction with the preterm infant. The study has both qualitative and quantitative elements.

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Authors' contributions

GKØ conceived the study, designed it, and drafted the manuscript. PIK participated in the study design and coordination, and helped to draft the manuscript. TU participated in the conception and formulation of the study design. SKC were involved in the conception and design of the study. GLG were strongly involved in the design of the intervention package. TU, SKC, GLG and LJ provided critical review and all authors provided final approval of the draft. All authors read and approved the final manuscript.

Competing interests

SKC and GLG are co-developers of the TIMP and partners in Infant Motor Performance Scales, IIC. The authors proclaim that there are no other conflicts of interests.

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Appendix III

Detailed Assessment of General Movements (GMs) During Preterm and Term Age

Name		**Date of Birth**	
Recording Date		**Postmenstrual Age**	weeks
Behavioural State (Coincidence)	☐ State 2 (Active Sleep)	☐ State 4 (Active Wakefulness)	

Global Assessment	☐ Normal	**Sequence**	☐ 2 variable
	☐ Poor Repertoire		☐ 1 monotonous and/or broken
	☐ Cramped-Synchronised		☐ 0 synchronised
☐ Hypokinetic	☐ Chaotic		☐ 0 disorganised

Detailed Scoring

	Neck	**Trunk**
	☐ **2 involved in the sequence**	☐ **2 fluent and elegant rotations**
	☐ **1** hardly or not involved	☐ **1** just a few rotations
		☐ **0** almost no rotations

	Upper Extremities	**Lower Extremities**
Amplitude	☐ **2 variable, full range**	☐ **2 variable, full range**
	☐ **1** predominantly small range	☐ **1** predominantly small range
	☐ **1** predominantly large range	☐ **1** predominantly large range
	☐ **1** neither small nor large but monotonous	☐ **1** neither small nor large but monotonous
Speed	☐ **2 variable**	☐ **2 variable**
	☐ **1** monotonously slow	☐ **1** monotonously slow
	☐ **1** monotonously fast	☐ **1** monotonously fast
	☐ **1** neither small nor fast but monotonous	☐ **1** neither small nor fast but monotonous
Spatial range	☐ **2 full space variably used**	☐ **2 full space variably used**
	☐ **1** limited space	☐ **1** limited space
	☐ **0** in one plane only	☐ **0** lifted-released
Proximal rotatory components	☐ **2 present, fluent and elegant**	☐ **2 present, fluent and elegant**
	☐ **1** just a few rotations	☐ **1** just a few rotations
	☐ **0** almost no rotations	☐ **0** almost no rotations
Distal rotatory components	☐ **2 present, fluent and elegant**	☐ **2 present, fluent and elegant**
	☐ **1** just a few rotations	☐ **1** just a few rotations
	☐ **0** almost no rotations	☐ **0** almost no rotations
Onset	☐ **2 smooth and fluctuating**	☐ **2 smooth and fluctuating**
	☐ **1** minimal fluctuations	☐ **1** minimal fluctuations
	☐ **0** predominantly abrupt	☐ **0** predominantly abrupt
Offset	☐ **2 smooth and fluctuating**	☐ **2 smooth and fluctuating**
	☐ **1** minimal fluctuations	☐ **1** minimal fluctuations
	☐ **0** predominantly sudden release	☐ **0** predominantly sudden release
Tremulous movements	☐ **2 absent**	☐ **2 absent**
	☐ **1** unilaterally present	☐ **1** unilaterally present
	☐ **0** bilaterally present	☐ **0** bilaterally present
Cramped components	☐ **2 absent**	☐ **2 absent**
	☐ **1** occasionally present	☐ **1** occasionally present
	☐ **0** predominantly present	☐ **0** predominantly present

Optimality subscores	**Upper extremities (max 18)**		**Lower extremities (max 18)**	
	Neck and Trunk (max 4)		**Sequence (max 2)**	

GM Optimality Score (max. 42) ⌊_⌋⌊_⌋

Paper I

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

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ABSTRACT

Objective: To examine test–retest reliability of the TIMPSI in infants at risk for impaired functional motor performance.
Methods: The TIMPSI was administered twice to 51 infants from two different hospitals in Norway.
Results: The intra-class correlation coefficient was 0.99.
Conclusion: Test–retest reliability of the TIMPSI was excellent.

1. Introduction

Motor assessments in infants at risk for developmental delay are primarily performed to discriminate between typically developing infants and infants with suspected neurological dysfunction. This is important when planning intervention, predicting motor difficulties and evaluating change over time [1,2]. In order to direct resources towards infants likely to gain most from intervention, while avoiding intervention on infants with typical development, it is essential that assessment tools are reliable and valid. The prevalence of developmental difficulties in infants born preterm increases with decreasing gestational age at birth (GA) [3], and the incidence of motor disabilities such as cerebral palsy and developmental coordination disorder is particularly high [3–5]. Systematic reviews of neonatal assessments tools conclude that the Test of Infant Motor Performance (TIMP) is one of the best motor assessment tools to discriminate between infants with age-appropriate motor development and infants with delayed motor performance. Further it is also useful for planning interventions and evaluating change over time [1,2,6,7].

The TIMP was developed to assess functional motor performance in new-borns and infants from 34 weeks postmenstrual age (PMA) to 17 weeks corrected age (CA). Conducted at 3 months CA the TIMP was predictive of children's motor performance at 4-5 years, as measured by The Peabody Developmental Motor Scales [8]. A test–retest reliability study of the TIMP in 106 infants PMA 32 weeks to CA 16 weeks with varying risk and ethnicity demonstrated a high correlation between scores on two different days ($r = 0.89$) [7].

Average time to conduct the TIMP is 25–35 minutes, which for the youngest and most fragile infants may be too demanding. Therefore, a shorter version was developed, the Test of Infant Motor Performance Screening Items (TIMPSI) [6,9], for identifying infants for whom the full verison should be conducted. In a group of low birth weight infants between PMA 34 weeks and CA 17 weeks total TIMPSI scores correlated well with total TIMP scores ($r = 0.88$) [9]. A test–retest reliability study of the TIMPSI in infants at risk for long-term motor difficulties has not yet been carried out, but should be performed before routinely implementing this test for the assessment of fragile infants. We wanted to explore the clinical utility of the TIMPSI by investigating the stability in scores and the measurement error when the same tester conducted two consecutive tests. The aim of this study was to examine test–retest

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reliability of the TIMPSI in a group of infants at high to moderate risk for long-term motor developmental difficulties.

2. Methods and participants

This study used an observational design to investigate test–retest reliability of the TIMPSI within a period of three days. This specific time frame was chosen because developmental changes are expected to be minimal over such a short interval [7]. In order to generalise the findings to clinical work, infants between PMA 36–37 weeks and CA 12–13 weeks, with varying risk for neurologic diagnosis or motor delay, were recruited.

Between April 2013 to December 2014, fifty-one infants from two hospitals in Norway, the University Hospital of North Norway (n = 14) and St. Olavs Hospital, Trondheim University Hospital (n = 37), were recruited for this study. Infants with high or moderate risk for long term motor development difficulties were eligible for inclusion. High risk was defined as infants born prior to 28 weeks GA with a birth weight <1000 g, infants with Grade III or IV intraventricular haemorrhages or periventricular leukomalacias and term infants with severe asphyxia treated with hypothermia. Moderate risk was defined as GA from 28 to 33 weeks. Parents were required to understand Norwegian or English. Medically unstable infants, infants who had undergone surgery and infants with genetic syndromes were excluded. With the exception of holidays and periods when the testers were on leave, eligible infants were continuously recruited. The sample was a convenience sample depending on availability of infants and parents at two time points as well as testers.

The study protocol was reviewed by the Regional Committees for Medical and Health Research Ethics (REC) January 2012, which concluded that the study did not require approval but should be reported to the Data Protection Officer at the Hospital.

2.1. The assessment tool

The TIMPSI is comprised of 29 of the 42 items from the TIMP. There are observed items scored during the observation of spontaneous movements and elicited items designed to assess the responses to visual and auditory stimuli, handling and changes of position [6]. The test is divided into three subsets: a Screening set, an Easy set, and a Hard set. The Screening set consists of 11 items with rating scales from five to seven points, score range 0–51. All infants are first assessed with the Screening Set. Based on the raw score of the Screening Set, a second set of either 10 easier or 8 harder items is administered to obtain a total score for motor performance [6]. The Easy set has four dichotomously scored items and six items with a five- or six-point rating scale, score range 0-31. The Hard set has eight items: five dichotomously scored and three with a five-point rating scale, score range 0–17 [10]. The scores for the administered items are summed with higher scores indicative of better motor performance, maximum score 99. TIMPSI age standards are available in the TIMP manual [6] based on the motor performance of 990 U.S. infants [9]. Average scores for infants PMA 36-37 weeks is 42 (SD: 16) and 79 (SD: 13) for infants CA 12–13 weeks.

2.2. Procedure

One tester from each hospital participated. Both testers were experienced paediatric physiotherapists who had attended workshops on the TIMP and had been using the test regularly for several years. A physiotherapist unknown to the parents in the neonatal intensive care unit (NICU) or Follow-up clinic invited all parents of eligible infants to participate in the study and a written consent was obtained. Because we aimed to minimize the burden for each infant and parents, test 1 was administered as part of ordinary clinical practice, either at week 36–37 PMA or at week 12-13 CA. Approximately half of the infants were tested at week 36–37 PMA and half tested at week 12–13 CA. The infants should be in "State of arousal level" three (eyes open, no movements) or four (eyes open, large movements) according to Prechtl's States [11]. The ideal time of the day for most of the infants was following a period of sleep and before meals. Test 2 was carried out within three days after test 1. In case of two tests carried out on the same day, pauses of several hours between the tests ensured the infants were rested and in the proper behavioural state for testing. In addition, testers would not remember scoring details of the previous test.

2.3. Statistical analysis

Sample size was estimated a priori according to Walter [12]. With a power of 80% and a significance level of 5%, we needed 45 participants to achieve an intra-class correlation coefficient (ICC) ≥0.8. Normality of the data was examined by the Shapiro-Wilk test. Relative reliability between Test 1 and Test 2 for within-subject differences was assessed by calculating $ICC_{1,1}$ [13]. Relative reliability refers to consistent ranking of scores for an individual in a group by repeated measurements. Absolute reliability, the standard error of measurement, was calculated as the square root of the mean within-subject variance (S_W) [14,15]. S_W is expressed in the original measurement scale with a low value expressing a small degree of measurement error. The difference between a subject's measurement and the true value would be expected to be less than $1.96 \times S_W$ for 95% of the observations [14]. The difference between the two measurements for the same subject is then expected to be less than $\sqrt{2} \times 1.96 \times S_W = 2.77 \times S_W$ for 95% of the pairs of observations [14]. Bland Altman plot was used for verifying the consistency of the measurements [16]. This plot gives a graphical presentation of the differences between two tests plotted against the mean difference of the two tests allowing visual assessment of the scoring distribution and potential measurement bias [16]. The software IBM SPSS statistics version 22 was used to perform the statistical analyses.

3. Results

The mean time interval between Test 1 and Test 2 was 1 day (SD: 0.84). Thirteen (25%) of the infants had both tests administrated the

Table 1
Neonatal characteristics and age of subjects tested using the TIMPSI.

	High risk (n = 27)	Moderate risk (n = 24)	Total (n = 51)
Birth weight (grams): mean (SD)	1499 (1158)	1546 (292)	1524 (814)
Gestational age at birth (weeks): mean (SD)	29.8 (6.2)	30.4 (1.7)	30.1 (4.4)
Bronchopulmonary dysplasia: n (%)	12 (24%)	0 (0%)	12 (24%)
Abnormal caput ultrasound: n (%)	9 (18%)	4 (8%)	13 (25%)
Intracranial bleed Grade III or IV: n (%)	2 (4%)	0 (0%)	2 (4%)
Periventricular leucomalasia: n (%)	3 (6%)	2 (4%)	5 (10%)
Infants tested at postmenstrual age 36-37 weeks: n (%)	6 (12%)	21 (41%)	27 (53%)
Infants tested at post-term age 12-13 weeks: n (%)	11 (22%)	13 (25%)	24 (47%)

SD: Standard deviation.

Table 2
Intra-class correlation coefficient between Test 1 and Test 2 for all infants and for the two age groups when the tests were performed.

	$ICC_{1.1}$	95% CI	S_w	SDD
TIMPSI score for all infants (n = 51)	0.99	0.98–0.99	3.09	8.56
TIMPSI score for infants tested at postmenstrual age 36-37 weeks (n = 27)	0.94	0.87–0.97	3.49	9.67
TIMPSI score for infants tested at post-term age 12-13 weeks (n = 24)	0.93	0.84–0.97	2.55	7.06

ICC: intra-class correlation coefficient, CI: confidence interval, S_w: measurement error, SDD: smallest detectable difference.

same day. Sample characteristics are presented in Table 1. Forty-five (88%) of the infants were born at or before week 33 GA and six (12%) were born at term. Thirty-two (63%) were boys. One in four had abnormal caput ultrasound, most of them in the high risk group, and one in four had bronchopulmonary dysplasia.

The infants tested at week 36-37 PMA scored in the below average range based on the normative sample with an average total raw score of 31.8 (SD 10.3) [6]. Infants tested at week 12-13 CA scored within the average range for age, with an average total score of 76.1 (SD 7.4). Since in general the scores were normally distributed, $ICC_{1.1}$ could be used to assess the degree of correlation between repeated tests. $ICC_{1.1}$ was 0.99 for all infants, 0.94 for infants tested at week 36–37 PMA, and 0.93 for infants tested at week 12-13 CA (Table 2).

Measurement error (S_W) for the total TIMPSI score of all infants was 3.1 which implies that in 95% of the cases the measurement error will be within 3.1×1.96 which equals 6.07 points on the total TIMPSI score. When comparing two time points, the difference should exceed the smallest detectable difference (SDD) calculated as $2.77 \times S_W$ to be sure that there is a difference beyond measurement error [14]. For our study this means that the differences in scores would need to exceed 9.7 points in infants with PMA 36–37 weeks and 7.1 points in infants with CA 12–13 weeks to indicate that real change has occurred.

The Bland Altman plot (Fig. 1) shows the agreement between the tests at two time points. The mean differences of the two tests was close to zero which indicates a very high agreement. The scores from 48 (94%) infants fell within 1.96 standard deviations of the mean difference for all observations equally distributed above and below the zero point. Upon visual inspection no differences were found between infants tested on the same day and infants tested on two different days.

4. Discussion

This is the first test–retest reliability study of the Test of Infant Motor Performance Screening Items (TIMPSI) in infants at risk for developmental problems. A previous test–retest reliability study of the full version of the TIMP demonstrated high correlation using Pearson's *r* (0.89) [7]. A test–retest study of the TIMPSI in a study population of children with spinal muscular atrophy also demonstrated high correlation using Pearson's *r* (0.95) [10]. Pearson's *r* is a measure of linear correlation between two values [17], while the ICC provides estimates of both association and agreement. Because we used the $ICC_{1.1}$ we cannot directly compare our results with the two aforementioned studies. Our results showed ICC values ≥0.93, which indicate excellent relative reliability of the TIMPSI. Values of 0.7–0.8 are regarded as satisfactory but for clinical application values of 0.90 are desirable [18]. Additionally, we calculated absolute reliabilities by S_W, which was high, implying that for evaluative purposes change in total scores must be rather high to conclude that there have been real changes beyond typical development. Our results are consistent with the purpose of the TIMPSI, which is to screen development in order to determine whether a full TIMP should be administered for discriminative purposes. Furthermore, the TIMP rather than the TIMPSI should be used to evaluate changes over time.

The spread of the scores in the Bland Altman plot was evenly distributed with approximately 95% within the limit of agreement. Two of the three infants that fell outside the limits, were tested at PMA 36–37 weeks and had low scores on the two tests. This might indicate that for subjects with low scores there is less consistency. However, due to the low number of infants this finding cannot be generalized.

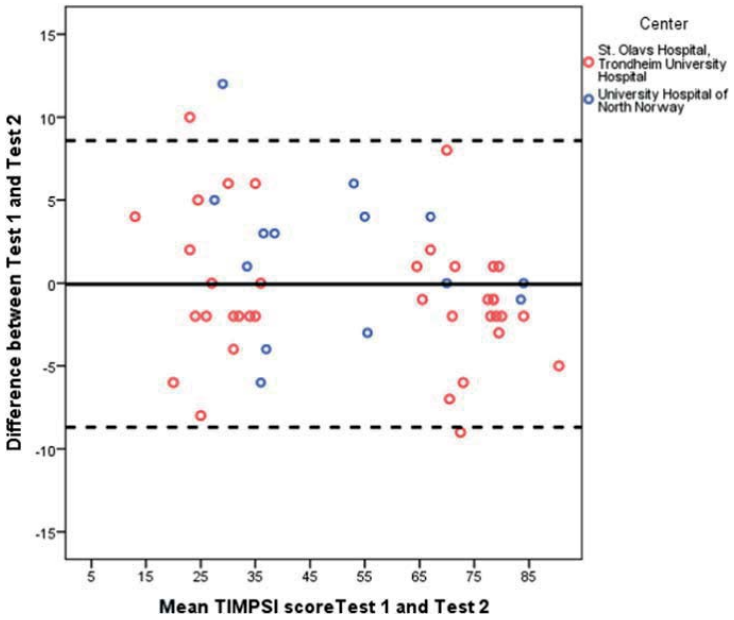

Fig. 1. Bland Altman plot of the difference against the mean of the TIMPSI scores on Test 1 and Test 2 with mean difference in solid line and ± 1.96 SD (95% of agreement) in broken lines. Squares represent infants from St. Olavs Hospital, Trondheim University Hospital, Norway, while circles represent infants from the University Hospital of North Norway.

Agreements and associations using the ICC in a group of infants with high to moderate risk of adverse neurodevelopment have not previously been reported. High ICC is likely if the infants' behavioural state is the same and the testers have high intra-rater reliability. Based on the ICC in this study, correspondence between the two tests was excellent, but the measurement errors were high. Variability between two tests can be caused by the instrument, the tester or the subject being tested. The infants were tested when they were in a satisfactory behavioural state and none or minimal change in motor development was expected during this period between tests.

One limitation of this study may be that some infants were assessed twice during one day. This is not ideal, but for participants living far from the hospital, this was the only possibility. When performing two tests on the same day, care was taken not to know the results from the first test when conducting the second test, for example, by assessing other infants between the two tests. The visual inspection of the data showed no differences between infants tested on the same or separate days.

Both testers were experienced paediatric physiotherapists with thorough knowledge of the test. Because only one tester from each hospital participated and the two hospitals are not located in the same area of the country, the testers assessed different babies. Consequently, we were unable to assess inter-rater reliability, which would have strengthened this study.

5. Conclusion

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.

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Paper II

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