Neurodevelopment and the effects of a neurobehavioral intervention in very preterm-born children
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Chapter 1

General introduction
Introduction

The general aim of this thesis is to expand the knowledge on long-term effects of an early intervention program for very preterm-born children, to provide optimal neurodevelopmental care and support for these vulnerable children and their parents.

Very preterm or very low birth weight infants

Preterm birth is defined by the World Health Organization as infants born before 37 weeks of gestation as measured from the last day of the last menstrual period. Infants less than 32 weeks’ gestation are classified as very preterm, and less than 28 weeks’ gestation as extremely preterm infants. Birth weight is also often used as an indicator for a neonate’s maturity, because not always gestational age is exactly known. Low birth weight infants are defined as infants with a birth weight less than 2500 grams, very low birth weight as less than 1500 gram, and extremely low birth weight infants as less than 1000 gram. In this thesis we focus on infants with a gestational age less than 32 weeks and/or a birth weight less than 1500 gram and we use the denomination “very low birth weight” (VLBW). Improved and technologically more advanced care in the neonatal intensive care unit (NICU) increased the survival rate of VLBW infants about 30% in the late nineties. In the Netherlands, 1.5% (n=2633) of all infants, born alive in 2012, were VLBW infants.

Factors that influence neurodevelopment in VLBW infants

During the last trimester of pregnancy the organization and myelination of the central nerve system (CNS) take place. The synaptogenesis of neuronal circuits is regulated by endogenous factors on the one side and sensory input and experience on the other side. Scientific research has proven that these early experiences during sensitive period of development plays an exceptionally important role in shaping the capacities of the brain and future functioning of the infant.

At 3 years of age, the child has about twice as many synapses as an adult. Those synapses that have been reinforced by virtue of repeated activation give rise to chemical changes that stabilize the synapses; the synapses that are not often used in early years, appear to be eliminated. A major ingredient in this process is the “serve and return” relationship between infants and their parents. Young infants naturally reach out for interaction through facial expressions, babbling and gestures and adults respond at them. These reciprocal and dynamic interactions of parental sensitive-responsiveness and child participation are essential for neurodevelopmental progression and literally shape the architecture of the developing brain.
There are factors, especially in VLBW infants, that have an adverse effect on brain- and neurodevelopment, so-called biological and environmental risk factors. Biology is a proxy for factors that determine the biologic make-up of the infant at birth and environment is a proxy for social and postnatal factors.\textsuperscript{10}

**Biological risk factors**

At the very important period of multiple brain developmental, the normal process of brain maturation is confronted with preterm birth and the untimely change from intra-uterine to extra-uterine environment. The immaturity of many organs and the combined effects of circulatory, respiratory, immunogenic and metabolic derangements play a role in the causation of brain injuries in VLBW infants. Cerebral complications with a high incidence are intraventricular hemorrhages (IVH) and periventricular leucomalacie (PVL). IVH occur in about 20\% of the VLBW infants, taken high and low severity presentation together, and varying degrees of cerebral white matter, PVL, even in 50\%.\textsuperscript{11} IVH and PVL occur isolated or in combination, and may both be accompanied by hydrocephalus. The brain injuries are affecting volume, integrity, and connectivity of the cerebral white matter, cortical grey matter, thalamus, basal ganglia, cerebral cortex, corpus callosum and cerebellum.\textsuperscript{12-14} These brain alternations, for their part, have negative influences on autonomic stability, state organization and motor maturation, and have profound implications for cognitive, motor, and behavioral functioning.\textsuperscript{14-17}

Several other biological risk factors play a role in the origin of altered brain maturation and brain injuries and, subsequent neurodevelopmental deficits, most importantly chronic lung diseases and infections. Bronchopulmonary dysplasia (BPD) has emerged in the past decade as the leading cause of chronic lung disease in infancy and develops in preterm neonates treated with oxygen and positive pressure ventilation.\textsuperscript{18} The pathogenesis is complex and results from injuries in the small airways that interfere with alveolarization and developing pulmonary vasculature. BPD affects at least one-quarter of infants born with birth weights <1500 gram, when defined as an oxygen need >28 days.\textsuperscript{19} The incidence of BPD, defined as an oxygen need at 36 weeks post menstrual age, is about 35\% for infants with birth weights <1500 gram.\textsuperscript{20,21} BPD is associated with damage of white matter and striato-thalamic structures, because of periods of hypoxia and hypercarbia, and a strong predictor of several long-term adverse health outcomes and cognitive and academic achievement.\textsuperscript{18,22-24}

Neonatal infections are also associated with poor neurodevelopmental and growth outcome in early childhood.\textsuperscript{25-27} About 24\% of the infants develop at least one episode of sepsis beyond day 3 of life and 50\% is treated for clinical or proven sepsis at least once during hospital stay.\textsuperscript{28,29} A small number of infants develop necrotizing enterocolitis (10\%) and meningitis (5\%).\textsuperscript{25,30} Sepsis is associated with the presence of pro-inflammatory
cytokines in the central nerve system, which has been shown to inhibit proliferation of neuronal precursor cells, activate astrogliosis, and stimulate oligodendrocyte cell death, all of which increase the risk of white matter damage. Also hypo-perfusion which often occurs during sepsis may play a role in the association between sepsis and neurodevelopmental sequelae.\textsuperscript{31}

**Environmental risk factors**

Biological factors account for only a portion of the variance associated with VLBW infant's long-term outcomes.\textsuperscript{32} There are several environmental factors to be taken into account. Pain and stress during the NICU-period of the infant, in addition difficulties to read behavioral signs of the infant, and parent-child interaction problems lasting into school age, lower social-economic class, and post-traumatic stress, depression and anxiety of the parents.

The influence of the environment of the VLBW infant, the parent-infant relationship and the impact of preterm birth on parents are considered as potential environmental risk factors.\textsuperscript{33,34} Social-economic status and educational level of the parents may have great influence on gravidity, and motor and cognitive development in VLBW infants.\textsuperscript{35,36} The environment of the NICU (including exposure to prolonged periods of light, unnatural noise, repeated disturbances and discomfort and pain from caretaking procedures, such as ventilation and punctures) causing frequently and persisting stress, can have a negative influence on the immature brain of VLBW infants.\textsuperscript{32,37}

The parent-infant relationship with the important ingredients of parental sensitive-responsiveness and child participation, is at risk after very preterm birth. Due to neurological immaturity and problems in self-regulation, VLBW infants are showing behavioral signals which are difficult to read for parents, such as less actively interactions, less eye contact, more gaze aversion, less positive facial expressions and less vocalization.\textsuperscript{38-40} Parents of VLBW infants have to put more effort to initiate and maintain interactions and they also receive fewer positive responds from their infants than parents of term-born infants.\textsuperscript{41}

For parents, preterm birth can be a difficult and distressing experience.\textsuperscript{42} Parents with VLBW infants reported more financial, social and family stress than parents of healthy term-born children.\textsuperscript{33,43,44} Between 26\% to 41\% of the mothers of VLBW infants reported post-traumatic stress symptoms.\textsuperscript{45} In addition, parenting a VLBW infant can be more demanding because of feeding problems, excessive crying and/or sleeping problems.\textsuperscript{46}
Consequences of preterm birth on neurodevelopment

VLBW infants are at great risk of major and minor disabilities. Although the incidence of severe handicaps, like cerebral palsy, deafness, blindness and severe mental retardation is decreasing slowly, VLBW infants still remain at great risk for a broad range of mild, often co-occurring, neurodevelopmental deficits.⁴⁷⁻⁵⁰ Long-term follow-up to school age revealed an even higher frequency of neurodevelopmental problems than in the first two years. Some deficits, such as problems with attention and hyperactivity and minor motor impairments, classified as developmental coordination disorder, are complex and may be subtle, but often tend to become more obvious at later ages.⁵¹⁻⁵³

Combinations of mild cognitive, motor and behavioral problems, with prevalence’s of up to 50 to 75%, are the dominant developmental deficits reported in VLBW infants.⁵⁴⁻⁵⁸ At 5 years of age, 45% of the children have mild neurological problems (minor neurological dysfunction), 39% have cognitive deficits, 30% have motor deficits and 27% have behavioral problems.⁵⁹ These deficits often persist throughout childhood and have a negative influence into adulthood because they crucially affect the child’s exploration of the world and involvement in academic and social activities. VLBW adults are three times more at risk for unemployment,⁶⁰ are less active during leisure time,⁶¹ and have more psychiatric disorders.⁶²

Self-regulation
Self-regulation is the infants competence to organize the behavior in order to gain control over his own body and the world around him.⁶³ Selfregulatory efforts are modulatory mechanism used by the infant to approach information and respond in an adaptive way, to cope with sensory input, or to protect himself from too much stimulation.⁶⁴ The altered connectivity in early brain development in VLBW infants, can disrupt the emergence of self-regulation, resulting in less opportunities to self-regulate and to react effectively on stimuli of the environment.⁶⁵,⁶⁶ Low self-regulation in VLBW infants lead to higher prevalence of difficulties in sustained attention, emotional regulations with both externalizing and internalizing behavioural problems, symptoms of impulsivity, inattention and executive dysfunctions, throughout childhood.⁶⁷⁻⁶⁹

Measurement of neurodevelopmental outcomes
To measure neurodevelopmental outcomes of VLBW infants, a heterogeneous group of neurodevelopmental assessments instruments are available. A systematic review of neuromotor assessments for preterm-born infants recommended the use of more than one assessment tool, in order to evaluate the efficacy of intervention programs in the first
Because children grow and develop over time, measuring developmental outcomes of children poses many challenges to choose the most appropriate measurement instrument.

Kirshner and Guyatt presented a methodological framework for assessing health indices, based on the need to distinguish between health states measurements instruments according to their purpose. They classified three categories. First, “discrimination”: referring to instruments that are designed to measure cross-sectional differences and required to be both reproducible and valid. Second, “prediction”: referring to instruments that are used as a diagnostic tool to predict developmental outcome and, third, “evaluation”: instruments that are designed to measure longitudinal differences within children over time, requiring an additional property namely responsiveness (or sensitivity to change).

Next to the goals and clinimetric properties of the instruments more practical issues, such as the time needed to administer the test and the age of preterm-born children play an important role in choosing the right instrument. Unfortunately, there are no single measurement instruments for cognitive or motor developmental outcome that cover all ages.

Assessment of cognitive and motor developmental outcomes

Intelligence is not one skill but a composite of multiple cognitive processes, including visual and auditory memory, abstract reasoning, complex language processing, understanding of syntax, visual perception, visual motor integration, visual spatial processing and speed processing. Cognitive assessments of very young infants are limited in their predictive ability to because of their reliance on assessments of visual motor and perceptual abilities. As children mature, more verbal and abstract cognitive abilities can be evaluated and scores more accurately reflect their specific abilities.

During the major part of the previous century, motor development was basically regarded as a neuromaturational process, but it became increasingly clear that motor development is largely effected by experiences. The neuromaturational theory proposes that changes in gross motor skills during infancy result only from the neurological maturation of the CNS. The dynamic motor theory considers the CNS as one of many subsystem that dynamically interacts to develop movements. Other elements that explain movement changes are the infant’s biomechanical and psychological factors, and the nature of the task or environment. The theoretical approaches of infant motor development formed the basis of various, currently applied instruments, evaluating the infants’ neuromotor development.
Early intervention programs

Early intervention refers to prevention-focussed programs occurring soon after birth. The distinctive feature of early intervention is that it starts when the plasticity of the brain is maximum instead of addressing problems at a later time and thus interventions are more likely to have maximal impact.78,79 Further advantages of early intervention programs are the influence of genetics, environment and experiences during sensitive periods of brain development which play an exceptional important role in shaping the capacities of the brain, like ‘wiring’ the highly integrated sets of neural circuits.80

In response to the high rate of neurodevelopmental deficits in VLBW infants, which persist throughout childhood, a variety of early intervention programs for preterm-born infants have been developed. The complex biological, medical, and environmental elements that contribute to early development have led to programs that encompass many different components, with services provided by a variety of disciplines.81 Early intervention programs differ in type of intervention (medical, neurobehavioral, paramedical, strength or weakness-bases), the focus of intervention (cognitive, motor, and/or behavioral development of the child, mother–infant interaction, parental psychosocial support, parent education), kind of interventionist (pediatrician/neonatologist, nurse, psychologist, pediatric physical therapist), location (hospital or home-based), and the timing, intensity and duration of program involvement.

In 2012, a Cochrane meta-analysis on the effect of post discharge early intervention programs for preterm-born infants concluded that interventions that focus on both the parent-infant relationship and on infant development have the greatest effect on cognitive development and a small effect on motor development at infant and pre-school age.82 Also other studies stated that positive outcomes are associated with parental sensitive-responsiveness, child participation, and infant’s competence to self-regulate.83-87 A systematic review suggest that home visiting for preterm-born infant promotes improved mother-infant interaction.88 However, there is a paucity of long term outcomes of randomized controlled trials involving multidimensional early interventions.

The Newborn Individualized Care and Assessment Program (NIDCAP) introduced by Als et al.89 in the mid-1980s is unique in its use of a combination of strategies in an attempt to address the different early developmental issues in the NICU.90,91 The underlying concept is designated the “synactive theory” to emphasize the simultaneous maturation and mutual interplay of the different subsystem of behavior throughout development.28 Three RCTs22-24 2 systematic reviews,95,96 and a Cochrane Review97 have reported positive short-term effects on medical outcome (duration on ventilation, supplemental oxygen supply, reduced incidence of IVH, BPD and reduced hospital stay), neurodevelopmental
outcome (improved self-regulation, motor, cognitive, behavioral development), less parenting stress and positive caregiving up to 12 months. A study with quantitative 3D-MRI techniques demonstrated beneficial structural changes in term NIDCAP infants in tissue distributions as well as development of white matter. But the sample size of all studies were small, shortcomings in design and methods were discussed and no evidence was found that the NIDCAP improves long–term neurodevelopment. Except for low risk preterm-born infants at 8 years where improved neuropsychological and neuroelectrophysiological function and brain structure was found.

IBAIP

The Infant Behavioral Assessment and Intervention Program© (IBAIP) is a post-discharge, preventive neurobehavioral intervention program which addresses both the infant and the parent at home. It is also based on the synactive theory of behavioral developmental organization. The program aims to support the infants’ self-regulatory competence and multiple developmental functions via responsive parent-infant interactions, focusing on environmental, behavioral, and early developmental factors. The IBAIP-trained interventionist evaluates the infant’s neurobehavioral organization and self-regulatory competence, within the context of the environment, and positively guides and supports the parents to sensitively and responsively interact with their infant. Facilitation strategies may be offered to best support the infant’s neurodevelopmental progression and self-regulation. The facilitation strategies address environmental facilitation (e.g. visual and auditory input), handling and positioning (e.g. the infant’s position in supine or prone), and cue-matched facilitation (e.g. hand to mouth, foot bracing, or hands to midline). The IBAIP aims to provide ample opportunities for the infant to actively process and explore information, while at the same time maintaining stable physiological and behavioral functioning. Thus the program supports the infant’s growth, the infant’s motivation to explore, and the possibility to learn from information. A detailed written report with individual recommendations is provided to the parents after every session.

The intervention is guided by the Infant Behavioral Assessment © (IBA). The IBA is an observational tool that systematically observes and interprets the developing infants’ neurobehavioral organization during interactions. Hundred and thirteen communicative behaviors are categorized according to four subsystems: the autonomic system, the motor system, the state system, and the attention/interaction system. Within each of the four subsystems, the behaviors are interpreted as approach (stable/engagement), self-regulatory, or stress (unstable/disengagement) behaviors.

The IBA is primarily intended to guide intervention strategies in infants from term to 8 months CA. The IBA does not have normative data but provides information on the quality and amount of information or support, appropriate for that particular infant at
that particular time. Reliability scoring of more than 85% is required during training. However, information on the clinimetric properties of the IBA was scarce.

The original RCT on the effects of the IBAIP

Between 2004 and 2007, a multicenter RCT was conducted in 7 hospitals in Amsterdam to compare the effects of the IBAIP to standard follow-up care, with respect to cognitive and motor development, infants’ behavioral regulation, the well-being of the parents, and parent-infant interaction. In this RCT, infants of gestational age (GA) <32 weeks and/or birth weight <1500 grams were included. Exclusion criteria were severe congenital abnormalities of the infant, severe physical or mental illness/problems of the mother, non-Dutch-speaking families for whom an interpreter could not be arranged, and participating in other trials on post discharge management. After computer-generated randomization, stratified for GA (< and ≥30 weeks) and recruitment site, with multiplets assigned to the same group, 176 VLBW infants were assigned to an intervention (90) or control group (86). The infants and the parents in the intervention group received 1 intervention session shortly before discharge and 6 to 8 sessions at home from an IBAIP-trained pediatric physical therapist up to 6 months CA. The control group received standard care.

Results of this study included improved cognitive, motor, behavioral development and mother-infant interaction at 6 months CA and improved motor development at 24 months CA in favor of the parents and infants who received the IBAIP intervention. Moreover, at 24 months CA, also improved cognitive development was found in high risk subgroups who received the IBAIP. A follow-up study at the preschool age of 44 months found improved independency in mobility in daily activities.

Follow-up study at 5.5 years

In a second follow-up study the effects of the IBAIP at school age were evaluated. Between 2009 and 2011, the parents of all children participating in the original RCT, were invited to the participate in the follow-up study at the age of 5.5 years CA. The pediatric and developmental assessments were performed at the follow-up clinic of the Academic Medical Center in Amsterdam. Cognitive abilities were assessed by a psychologist, motor development, visual-motor integration and, neurologic functions were assessed by a pediatric physical therapist (JvH). The investigators were blinded for group assignment. While their child was fulfilling the developmental assessments, the parents were asked to fill out a questionnaire regarding the behavior of their child. Sociodemographic data, school performances and the need for mental or paramedical support at 5.5 years CA were obtained by parental interview.
Assessment of cognitive development
At 6, 12, and 24 months CA, cognitive development was assessed with the mental scale of second Dutch edition of Bayley Scales of Infant Development (BSID-II-NL). At 5.5 years CA, the third Dutch edition of the Wechsler Preschool and Primary Scale of Intelligence (WPPSI-III-NL) was used. The BSID-II-NL age range is from 1 to 42 months and it can be used for discrimination and evaluation purposes. The WPPSI-III-NL, age range from 2.6 to 8 years, has the same purposes. In addition, components of intelligence, namely visual motor integration and coordination and processing speed were assessed with the Developmental Test of Visual Motor Integration (VMI) and tasks of the Amsterdam Neuropsychological Tasks (ANT).

Assessment of motor development
At 6, 12, and 24 months CA, motor development was assessed with the psychomotor scale of the BSID-II-NL. At 5.5 years CA, the second edition of the Movement Assessment Battery for Children (MABC-2) was used. The test construction of the BSID-II-NL is based on general maturational principles. The MABC-2 age range is from 3 to 16 years, its purpose can be discrimination or evaluation and its construct is based on the dynamic theory. In addition, the Alberta Infant Motor Scale (AIMS) was used at 12 months CA (in a subset of participating children), and the neurological examination according to Touwen at 5.5 years CA. The age range of the AIMS is from term age to 18 months, its purpose is discrimination and its construct is based on the dynamic theory. The age range of Touwen is from 4 to 18 years, its purpose is discrimination and it is based on the traditional neuropediatric neuromaturation concept.

Assessment of behavior
The Strength and Difficulty Questionnaire (SDQ), a parental behavioral screening questionnaire consisting of items hyperactivity/inattention, conduct problems, peer problems, emotional symptoms and prosocial behavior was used to evaluate the impact of behavior on motor development and on early intervention.
Aim and outline of the thesis

The general aim of this thesis was to expand the knowledge on long-term effects of an early intervention program for very preterm-born children, to provide optimal neurodevelopmental care and support for these vulnerable children and their parents.

The main objective of this thesis was to evaluate the effect of the Infant Behavioral Assessment and Intervention Program (IBAIP) on cognitive, motor, and behavioral development in VLBW infants at 5.5 years CA and longitudinally from 6 months up to and including 5.5 years CA.

Additional objective was to elucidate the relation between motor impairment and other developmental deficits in very preterm-born and term-born children at 5 years CA.

As the outcome of research depends on the quality of the assessment instruments used in a study, other objectives were to investigate the clinimetric properties of the Infant Behavior Assessment (IBA) in order to evaluate neurobehavioral organization from term to 6 months, and to compare the Alberta Infant Motor Scale (AIMS) and the Dutch second version of the Bayley Scale of Infant Development (BSID-II-NL) in their ability to detect intervention effects at 12 months CA.

Outline
Chapter 1 presents a general introduction on VLBW infants and early intervention, and objectives and outline of the thesis.

Chapter 2 and 3 focus on the developmental assessment instruments used in VLBW infants.

Chapter 2 describes the reliability, sensitivity and responsiveness of the IBA. Videotaped assessments of 176 VLBW infants participating in a RCT on the effect of the IBAIP (86 infants received the IBAIP, 90 infants received standard care), served to evaluate the standardized IBA observation.

Chapter 3 compares two motor developmental measurement instruments, the AIMS and the psychomotor scale of the BSID-II-NL, in their ability to evaluate effects of intervention in VLBW infants. At 12 months CA, 116 of the 176 VLBW infants participating in the RCT on the effect of the IBAIP, were assessed both with the AIMS and the BSID-II-NL. Intervention effects of the IBAIP on the AIMS and the psychomotor scale of the BSID-II-NL were compared.

Chapter 4 concerns motor impairments and associated developmental deficits in very preterm-born infants in comparison with term-born infants.
In Chapter 4 the relation between motor impairments and other developmental deficits was studied in a cohort of 81 children, born <30 weeks' gestation and/or birth weights <1000 gram, and 84 term-born children at 5 years CA. Motor impairments, assessed with the MABC-2, was compared between the groups and the relation between motor impairments and other developmental deficits, assessed with the neurologic examination of Touwen, WPPSI-III-NL, processing speed and visuomotor coordination tasks of the ANT and the SDQ, between the groups. Subsequently a mediation model was tested to analyze the extent to which these deficits mediate the association between preterm birth and motor impairments.

The last part of the thesis, chapter 5 and 6, concerns the intervention effects of the IBAIP at 5.5 years and over time.

Chapter 5 presents the results of the IBAIP on cognitive, neuromotor and behavioral development in VLBW infants at 5.5 years CA. In the RCT, 86 VLBW infants received IBAIP intervention until 6 months CA and 90 VLBW infants received standard care. At 5.5 years CA, 69 IBAIP children and 67 control children were assessed with the WPPSI-III-NL, the MABC-2, the VMI, the neurologic examination of Touwen and the SDQ.

Chapter 6 investigates the longitudinal effects of the IBAIP in VLBW infants on cognitive and motor development from 6 months up to and including 5.5 years CA. At 6, 12, and 24 months CA, cognitive and motor development were assessed with the BSID-II-NL. At 5.5 years CA the WPPSI-III-NL and the MABC-2 were used. Longitudinal data were analyzed with linear mixed models in the total group of 176 VLBW infants and in three subgroups with biological or environmental or a combination of biological-environmental risk factors.

Chapter 7 presents the general discussion, in which the findings and limitations of this thesis are further emphasized and implications for clinical practice and recommendations for future research are given. Finally, the results of the studies presented in this thesis are summarized.
References


