Neurodevelopment and the effects of a neurobehavioral intervention in very preterm-born children
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Chapter 7

General discussion
Very preterm birth has adverse effects on the normal maturational process of the brain, which consequently may result in neurodevelopmental deficits in VLBW infants. These deficits often co-occur and persist throughout childhood.1-4

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 Infant Behavioral Assessment and Intervention Program© (IBAIP) is an early intervention program, aiming to prevent developmental deficits in VLBW infants by supporting both the infant’s competence to self-regulate and the parental sensitive-responsiveness.5 Between 2004 and 2007 a multicenter randomized controlled trial (RCT) was carried out to compare the effects of the IBAIP to standard care at 6 and 24 months CA.6,7 A follow-up study between 2007 and 2009, evaluated the effects of the IBAIP at the preschool age of 44 months.8 In a second follow-up study, between 2009-2011, the effects of the IBAIP at early school age (5.5 years CA) were evaluated.

The specific objectives in this thesis were:
- To investigate the clinimetric properties of the Infant Behavior Assessment (IBA) in order to evaluate neurobehavioral organization in VLBW infants (Chapter 2).
- To compare two motor assessment instruments, the Alberta Infant Motor Scale (AIMS) and the psychomotor scale (PDI) of the second Dutch edition of Bayley Scales of Infant Development (BSID-II-NL) in their ability to detect intervention effects at 12 months CA (Chapter 3).
- To elucidate the relation between motor impairment and other developmental deficits in very preterm-born children and term-born children at 5 years of age (Chapter 4).
- To evaluate the effect of the 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 (Chapter 5 and 6).

In this concluding chapter, the main findings of the 5 presented studies are discussed and issues concerning the methodology are critically reviewed. Clinical implications and suggestions for further research conclude this final chapter.
Main findings of the study

Developmental assessment instruments
The IBA is a measurement tool assessing self-regulation in infants from term age to 9 months CA. Because the IBA is primarily intended to be used in a qualitative manner, in conjunction with the IBAIP, the clinimetric properties of the IBA needed to be further investigated, by determining its reliability, sensitivity and responsiveness to evaluate neurobehavioral organization (i.e. self-regulation).

In Chapter 2, we showed that the reliability, sensitivity and responsiveness of the IBA are satisfactory to good to evaluate neurobehavioral organization in VLBW infants. The inter-observer reliability of the IBA was moderate to good and the item-by-item percentage agreement was good to excellent. The sensitivity of the IBA was demonstrated by clear and expected differentiations in neurobehavioral organization between VLBW infant with or without biological high risk factors (gestational age ≤28 weeks or bronchopulmonary dysplasia (BPD)) at 35-38 weeks postmenstrual age. Large responsiveness was found on all scores of the IBA in both the intervention and control groups and in the BPD high-risk subgroups over a 6-month period.

Because of the fact that the IBA give insight in how to support the infant's self-regulation during interactions from minute to minute, distinguishes the instrument from other neurobehavioral assessments at infant age. Those instruments provide a degree of self-regulation but not an entry for support. Supporting the infants' self-regulatory competence to approach and respond to environmental information and to diminish stress is currently seen as an important element in early intervention for infants at biological and/or social risk. A behavioral analysis of the child's individual expectations, like the IBA, might be the basis for effective neurobehavioral intervention. Moreover, neurobehavioral analyses may have been crucial for the positive results we found in our RCT in VLBW infants, as it was the basis for intervention. Complementary use of a neurobehavioral analyses instrument to neurological and developmental measures provides a more comprehensive picture of the infants' development.

In the light of the need for sensitive assessment tools that measure changes in infant development, we demonstrated that two motor assessment tools differ in evaluating neurobehavioral intervention effects in VLBW infants at 12 months CA (Chapter 3).

Both the AIMS and PDI of the BSID-II-NL found intervention effects in VLBW infants at 12 months CA. However, a reduction of abnormal motor development was reflected only on the AIMS, and the responsiveness of the AIMS to detect intervention effects was better than that of the PDI. The AIMS classified 13.8% of the infants in the intervention
group as having an abnormal motor development versus 27.6% of the infants in the control group, while the PDI classified 1.8% versus 3.5% respectively. The failure to detect motor disturbances at early age may be due to the lack of sensitive measures at that age, and may be one of the reasons for the apparent increase in developmental problems with increasing age in VLBW infants. Therefore, caution is recommended in monitoring VLBW infants only with the PDI, and the additional use of the AIMS is advised when evaluating intervention effects on motor development at 12 months CA.

Further, we showed that the AIMS detected more specific intervention effects than the PDI, and pointed towards effects on especially postural control. The subscales of the AIMS can be useful to elucidate specific effects of an intervention on the motor system and moreover, the subscales provide more detailed possible motor disturbances. Researchers and interventionists may gain better insight into the gross motor development by using the AIMS than the PDI of the BSID-II.

Motor impairment and associated deficits
Preterm birth is associated with motor impairments persisting throughout childhood.14 To elucidate the relation between motor impairment and other developmental deficits, we compared a group of very preterm-born (<30 weeks’ gestation and/or birth weights <1000 grams) and a group of term-born (>37 weeks’ gestation and birth weights >2500 grams) children at 5 years CA (Chapter 4).

Our study confirmed the high frequency of neurodevelopmental impairments in very preterm-born children compared to their term-born peers at 5 years CA. However, we found that very preterm-born children with motor impairments had other developmental deficits more often as well, compared to very preterm-born children without motor impairments. Especially complex minor neurological dysfunctions (MND) and impairments in cognition, processing speed and visuomotor coordination occurred more often. Motor impairments in term-born children was not associated with the other developmental deficits.

Further, we found that 4 developmental deficits, complex MND, low IQ, slow processing speed and hyperactivity/inattention, mediated the relation between preterm birth and motor outcome. Complex MND, which can be considered as a distinct form of perinatally acquired brain dysfunction, is associated with damage to the cortico-striato-thalamo-cortical and cerebello-thalamo-cortical pathways.15 Especially these brain circuitries are vulnerable in very preterm-born children and are mutually involved in both cognition and motor performance.16,17
Intervention effects of the IBAIP at 5.5 years and over time

The IBAIP led, 5 years after the last intervention session, to improvements on performance IQ, ball skills, and visual-motor integration in VLBW infants at 5.5 years CA (Chapter 5). The IBAIP did not improve behavior at this time-point.

Thus, cross-sectional data-analyses revealed significant intervention effects of the IBAIP on cognitive development at 6 months and 5.5 years corrected CA, and on motor development at 6, 12 and 24 months and 5.5 years CA. However, this approach is insensitive to individual developmental changes over time, and mean outcomes of the study groups may therefore not be representative for the patterns of individual outcomes. To our knowledge, no longitudinal data-analysis of outcomes of early intervention studies, has been reported. Therefore, we additionally evaluated the intervention effects of the IBAIP longitudinally from 6 months up to and including 5.5 years CA (Chapter 6).

We found that the IBAIP leads to long-term improvements on motor development in VLBW infants. However, a longitudinal intervention effect on cognitive development was not found.

We found that VLBW children with BPD benefitted longitudinally the most from the intervention, both on the cognitive and motor domains. Low maternal education did not influence intervention effects over time; but in children with multiple risks (low maternal education and abnormal cranial ultrasound or BPD) a longitudinal intervention effect on cognitive development was found.

The IBAIP may protect or can help to reorganize the vulnerable brain structures in VLBW infants because the improvements on performance IQ, ball skills, and visual-motor integration, found at 5.5 years CA, all involve visual-spatial abilities and motor responses, and functionally overlap to a large extend. The most common brain injuries in VLBW infants, as described in Chapter 4, are related to complex MND, problems in processing speed and, visual-spatial and motor impairments.16,20,21

VLBW children with BPD benefitted the most from the IBAIP. BPD is associated with damage of white matter and striato-thalamic structures, because of periods of hypoxia and hypercarbia.22-24 Also, BPD has long-term adverse effects on cognitive and academic achievements above and beyond the effects of VLBW.25 At 5.5 years CA, 59.5% of the VLBW children with BPD in our cohort had complex MND versus 14.9% of the VLBW infants without BPD. In the total intervention group 34.8% had complex MND versus 58.6% of the intervention children with BDP. This indicates that the children with BPD had more damage in the above mentioned circuitries and that the IBAIP is especially effective in improving development of VLBW infants with BPD.
It is assumed that qualitative good interactions between parent and child, accomplished in early childhood, will continue in time and positively affect infants development. Strengthening the parental sensitive-responsiveness and supporting the child’s self-regulation in an early and sensitive period of brain development, possibly have resulted in the sustained improvement at 5.5 years CA and earlier time-points. We hypothesized the following underlying mechanisms: (1) improving early self-regulation may affect the motor system because the self-regulatory strategies offered, enhances midline orientation which strengthens the child’s control over posture and movements; (2) the strength-based and scaffolding neurobehavioral support of the interventionist and parent to the child. Strength-based support means building on the strengths of both the child and parents. It is a positive approach to the child and parents, seeking for possibilities instead of problems in behavior. Scaffolding support implies the process in which parents continuously adjusts their interactions to the infant's changing needs for support over time. The strength-based support may improve the parents’ self-confidence and, parents’ scaffolding efforts enhances the infants’ information processing and abilities to explore.

The IBAIP versus comparable programs

Three intervention programs are comparable with the IBAIP because they also focus on parent-infant interactions and infant development: the Norwegian modified Mother-Infant Transaction Program (mMITP), the British Avon Premature Infant Project (APIP), and the Australian Victorian Infant Brain Study-Plus (VIBeS-Plus). They all found improvement in aspects of cognitive development. Only the IBAIP has led as well to cognitive as to motor improvements, although the duration of intervention was short compared to the other early intervention programs. The timing of the intervention, the specific sensitive-responsive parent-infant approach of the IBAIP, and supporting the child’s self-regulation to improve development, may be crucial in that respect.

In addition to the duration of the intervention, other differences which may contribute to different outcomes between the early intervention studies were: (1) composition of the patient groups; (2) composition of the control groups; (3) profession of the interventionists, and (4) the length of follow-up.

In recent literature, the importance of supporting the parent in their mediation role, is more and more emphasized. The extra psychological support in the mMITP and VIBeS-Plus may have contributed to less parental stress and depression and less behavioral problems of the infant. Although no effect on maternal psychological distress was found in the first 2 years after the IBAIP was given, increased maternal sensitivity in interaction with their VLBW infant was found. At 5.5 years CA, we found no positive intervention effects on behavior.
On both the mMITP as the IBAIP, a delayed intervention effect on cognitive improvement was found. It remains speculative whether this delayed effect results from methodological differences, insufficient sensitivity of measurements to reveal subtle differences in cognition at earlier age or is related to the maturation process of the involved brain areas. Aspects of mental function mature at different times in a child’s life and synapse formation of higher cognitive capacities begin to mature by age 3 years.27 In chapter 4, we found that motor outcome in VLBW infants is strongly related with cognitive outcome. Others demonstrated that several cognitive tasks (working memory, processing speed, visual processing) are interrelated with motor tasks (coordination, fine manual skills) in children without developmental delays.39,40 This indicates a common neuro-anatomical background of processes in complex cognitive and motor actions.

Methodological considerations

Developmental assessment instruments

Correcting for prematurity or not

In literature there is no consensus about until what age, the age should be corrected for prematurity. According to the BSID manuals, correction for prematurity should be applied as long as 24 months postnatal age.12,41 The American Academy of Pediatrics recommends that test scores should be corrected for prematurity up to 3 years of age because it is assumed that at later ages VLBW infants catch up to their chronological same-age peers.42 But Wilson-Ching et al.43 found substantial lower scores in cognitive developmental tests in the pre-school and school-age years in preterm infants and they suggested that for research purposes, correcting beyond age 3 is necessary because it removes an important bias against those born preterm. There can be a great risk of misinterpreting change over time if corrected age is employed in early assessments but chronological age is used beyond age 3. We decided to assess the VLBW infants at their corrected age in the studies presented in this thesis. In the study described in chapter 4, we found substantial differences in all developmental domains between very preterm-born children, using the corrected age, and term-born children at the disadvantage of the very preterm-born group. If we had used the chronological age, these difference would have been even bigger, indicating that at age 5 preterm-born children did not catch up to their chronological same-age peers.

Normative data

We used the normative Canadian data of the AIMS because no Dutch norms are available (Chapter 3). Psychometric properties of a developmental test might be influenced by culture-specific elements. Previous studies have shown that, unlike infants in North
America, infants in Europe are predominantly placed in prone position to sleep, which has led to later attainment of early motor milestones, such as rolling over and sitting up.44,45

In 2006 a norm scale for preterm infants was introduced because the gross motor developmental profile of preterm infants may reflect a variant of typical gross motor development, specific for this population.46 The consequence of using the preterm norm scale is that infants with mildly abnormal motor development will be classified as normal whereas, especially in the very preterm group, a high incidence of mild, often co-occurring, neurodevelopmental problems have been found at 5 years of age.3 Moreover, preterm AIMS scores were not investigated in relation to 5 years’ motor outcome. Therefore, we chose to use the general population scores of the AIMS to compare with.

Questionnaires
No significant intervention effect was found on behavior at 5.5 years of CA (Chapter 5). In both groups, 10.8% of the parents reported behavior difficulties in their children. This is low compared to other studies in very preterm-born children.3 We only used the parents’ form and not the teachers’ form of the SDQ, and this may have led to an incomplete representation of this domain. The psychometric properties of the SDQ are strong, but the reliability of the teacher form seems stronger compared to that of the parent form.47 This may be explained by the different nature of the relationship with the child and different contexts, where different behaviors are shown. According to a recent study, investigating the validity of multi-informant reports of the SDQ in preterm infants, multi-informant reports are the best for detecting attention deficit hyperactivity disorder, and emotional or conduct disorders.48 Unfortunately, we did not apply these reports in our follow-up at age 5.5 years.

Motor impairment and associated deficits
We studied the associations of motor impairment with other developmental deficits in a cohort of 81 very preterm-born and 84 term-born children at 5 years of CA (Chapter 4). Term-born children were recruited from the school or social network of the very preterm-born group or via mainstream schools in the neighbourhood of our hospital. Excluded were children of the term-born group with a planned or current referral for learning or behavioral problems. This strategy enabled us the comparison with normal developing children but not with term-born children with learning or behavioral problems.
Intervention effects of IBAIP at 5.5 years and over time

Statistical issues

The strengths of the early intervention study is that all group comparisons were done within the design of a randomized controlled trial. However, despite random assignment, more infants in the intervention group received respiratory therapy (i.e. surfactant treatment, continuous positive airway pressure and oxygen therapy ≥28 days). In addition, occurrence of septic periods and need for indomethacin was higher in the intervention group. This inequality remained at all follow-up time-points and formed a disadvantageous issue in this trial. The between group differences have been statistically adjusted, as these perinatal characteristics are known to influence neurodevelopment (Chapter 5, 6). Only after these corrections, positive intervention effects were found.

A limitation inherent to follow-up studies is attrition bias. The response rate at 5.5 years CA was 80% in the intervention group and in the control group 74%. This was reasonable, taken into account that the cohort was drawn from a multicultural, urban population, in which education was low in 38% of the parents. Nevertheless, we had sufficient power (82%) to detect possible differences between the intervention and the control group. The assessed children did not differ from the non-participants with respect to sociodemographic and perinatal factors, except that mothers of participants were more often born in the Netherlands than those of the non-participants. Therefore, we assumed that the results of the assessed cohort could be generalized to the total cohort of VLBW infants.

Longitudinal data analysis and test characteristics

There are no comprehensive cognitive or motor developmental tests that can be applied from infancy to childhood and therefore, different instruments for both cognitive and motor development were used in the longitudinal data analysis (Chapter 6). In our study, only total IQ effects on cognitive development could be analyzed over time, because the mental scale of the BSID-II-NL does not have a verbal and performance separation, as in the WPSSI. That is unfortunate because intervention effects at age 5.5 were found for performance and not total IQ. The mental and motor scale of the third version of the BSID\(^41\) has now 5 subscales; fine and gross motor, language (receptive and expressive) and cognitive development. Further research is warranted to investigate the correlation between cognitive outcomes on the BSID-III and the items of the WPPSI and also on motor outcomes of the BSID-III and the MABC-2 items in VLBW children.
Clinical Implications

Developmental assessment instruments
As self-regulatory competence of a child plays a key role in cognitive, motor and behavioral development, a neurobehavioral analyses should be considered to be used complementary to currently used other infant assessments. Not only to denominate intervention goals, but also in neonatal follow-op assessment protocols in the first year. The IBA is a reliable and valid tool (Chapter 2) that gives a better insight into the infant's developmental goals or underlying problem areas and may contribute to the professional's understanding and evaluation of the self-regulatory competence and abilities to participate in interactions.

The AIMS should be added to the neonatal follow-up protocol to assess motor development in VLBW infants from term age to 18 months of age. In Chapter 4 we found that this instrument is superior in finding motor impairments than the more often used PDI of the BSID-II-NL. Furthermore, the instrument has the advantage of incorporating other motor developmental elements like the gravitational position of the infant, weight bearing and postural alignment. These are necessary elements to observe in VLBW infants because they are known to experience difficulties in these qualitative aspects of motor development, because of reduced active flexion power and discrepancies between the active and passive muscle tone.49,50

Motor impairment and associated deficits
Long-term follow-up of VLBW children after discharge from hospital throughout their school career should be implemented, in order to identify those children in need for support. Neonatal follow-up differs by hospital. In general the duration of neonatal follow-up is 2 years. However, the follow-up of very preterm-born children at age 5 revealed a high frequency of co-occurring mild developmental impairments in different domains (Chapter 4). It is important to recognise that especially very preterm-born children with motor impairment are also highly likely to have more often complex MND and low IQ, slow processing speed and visuomotor coordination problems than very preterm-born children without motor impairment. At age 5, the task complexity increases and information processing becomes more important. Therefore, mild impairments become more noticeable and a burden at school-age. The combination of problems decreases the potential to compensate and puts these children at risk for later learning disabilities and social problems.1 Therefore, other deficits should be taken into account, when very preterm-born children are referred for motor impairment.
Intervention effects of IBAIP at 5.5 years and over time

Due to improved and technologically more advanced care on the neonatal intensive care unit (NICU) and the lowering of the limit of active intervention to 24 weeks gestational age in the Netherlands, more preterm-born children do survive. However, they are longer exposed to risk factors, that may have an adverse effect on brain- and neurodevelopment. Therefore, the focus on healthy survival of preterm-born children remains very important, and should include optimal neurodevelopmental care and support for these children and their parents. Combining NICU-based interventions, such as done in the Caffeine for Apnea of Prematurity (CAP) trial\textsuperscript{51,52} to reduce biological risks, and to support the parent-infant relationship and infant development as done in the IBAIP, will reinforce the positive neurodevelopmental outcomes because biological factors account for only a portion of the variance associated with VLBW infant’s long-term outcomes.\textsuperscript{53}

An increase in the duration of the IBAIP will possible lead to more cognitive gains if the intervention have an extension in the most sensitive period of cognitive development. No improvements, based on individual developmental outcomes over time, on cognition, except for the subgroup of VLBW infants with BPD, were found (Chapter 6). Possibly, because the intervention was given in the relative short period of 6 months after discharge from hospital.

More attention should be given to the well-being of the mother and/or father, especially in social risk families, because this may strengthen the resources and capabilities of the parents to achieve a sensitive and responsive parent-child relationship. To obtain more positive effects of the IBAIP on behavior and in children with low educated mothers, adding the support of a psychologist to the intervention is recommended.

The results of the studies on the effects of the IBAIP have led to the implementation of an early intervention program for VLBW infants in the Netherlands. The period of intervention has been extended to 12 months CA after discharge from hospital and more attention will be given to the mental well-being of the mother.

Conclusion and suggestions for future research

The IBAIP effectively supports the neurodevelopment of VLBW infants until 5.5 years of CA. VLBW infants with BPD benefitted most from the early intervention. The results of the studies on the effects of the IBAIP have led to the development and implementation of an early intervention program in the Netherlands. The outcomes of this so-called ToP program (Transmurale Ontwikkelingsondersteuning voor Prematuur geboren kinderen en hun ouders, translated: transmural developmental support for preterm infants and
their parents), needs to be evaluated in future research in order to determine if the ToP intervention elements, like the duration of the program until 12 months and psycho-education, further improve effective developmental care and support for VLBW children and their parents.

Strengthening the parental sensitive-responsiveness and the child’s self-regulation in an early and sensitive period of brain development, underlies the effects of neurodevelopmental improvement by the IBAIP. Future research is warranted to determine if parental sensitive-responsiveness and self-regulatory competence in other infant populations, with biological and environmental factors contributing to the risk of disabilities, are also the key elements to support and improve long-term neurodevelopmental outcomes.

The clinimetric properties reliability, sensitivity and responsiveness of the Infant Behavioral Assessment (IBA) are satisfactory to good to evaluate and support neurobehavioral organization (i.e. self-regulation) in VLBW infants. However, research use of the IBA requires a careful creation of the sample interaction for each specific infant group and/or age. Therefore, additional validation of the IBA in different infant populations and at different ages is warranted.

Although the scores indicate an acceptable consistency with which different observers can create the same analyses of infant behavior, some refinement of the IBA definitions may be needed. Differences in scoring may occur when the infant displays the behavior for a very short moment, or as part of another movement. Adding a time component to the definitions of some of the motor items of the IBA may further enhance inter-observer agreement.

Since the abilities in which VLBW infants’ experience difficulties as trunk control and trunk rotation, are underrepresented in both the second and third version of the BSID, future research is needed in order to develop a set of neurodevelopmental assessment instruments that are able to assess long-term neurodevelopment in VLBW infants. A first step is to investigate the correlation between the AIMS and the motor scores of the third edition of the BSID, as well as between AIMS scores and motor outcomes of the MABC-2 at school age.

How cultural differences might affect the administration of the AIMS, needs to be investigated by establishing Dutch norm values of the AIMS.

The clinical implication of differences between corrected and uncorrected developmental outcomes in children with different low gestational ages at different time-points in childhood needs further study, in order to obtain agreement until when correcting for prematurity.
References


