Uitnodiging
Voor het bijwonen van de openbare verdediging van het proefschrift VISUAL IMPRINTS OF VERY PRETERM BIRTH Evidence for cerebral visual impairments in very preterm born children op vrijdag 30 oktober 2015 om 11.45 uur in de aula van de Vrije Universiteit, De Boelelaan 1105 te Amsterdam Aansluitend bent u van harte welkom op de receptie
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Chapter 7
Summary and General Discussion
The main aims of this thesis were to extend insight into visual functioning of very preterm/very low birth weight (VP/VLBW) children, including oculomotor, visual sensory and visual perceptive functioning. In addition, we aimed to study associations between deficits in these visual functions and behavioral and motor functioning. To meet these aims, studies were undertaken 1) to clarify previous heterogeneous findings on visual perceptive and visual-motor integration dysfunctions in very preterm born children, 2) to establish a comprehensive profile of visual functioning in VP/VLBW children using a wide range of measures of oculomotor, visual sensory as well as visual perceptive functioning, 3) to extend the profile of visual functioning with measures of visual attention and visual-motor integration performance, 4) to define cerebral visual impairment (CVI) using clear cut empirical criteria derived from the visual assessment outcomes, and evaluate its validity against measures of intellectual and behavioral functioning, and 5) to investigate the visual correlates of motor performance of VP/VLBW children. The main results are summarized in Table 1.

**SUMMARY OF MAIN FINDINGS**

In a systematic review using meta-analytic techniques, evidence was found for substantial dysfunctions in visual perceptive as well as visual-motor integration functioning in VP/VLBW children (chapter 2). Results were derived from 16 studies covering a total sample of 1478 VP/VLBW children, indicating selective rather than global effects of VP birth/VLBW on visual perceptive functioning. Specifically, visual-spatial perception was found most affected, as indicated by medium to large-sized differences between VP/VLBW and term born children on the Judgment of Line Orientation ($d = 0.60$) and NEPSY Arrows tests ($d = 0.92$), respectively. Measures reporting a composite score consisting of multiple visual perceptive abilities provided inconsistent findings (Motor-free Visual Perception Test $d = 0.10$, Test of Visual Perceptual Skills Revised $d = 0.72$). Since these meta-analytic results are based on a small number of studies for each of the tests, the findings should be cautiously interpreted and await replication in future studies. In addition, the measures eligible for meta-analysis only tapped into few visual perceptive abilities, highlighting the need to extend the range of measures employed to further unravel visual perceptive problems in VP/VLBW children. Furthermore, our meta-analytic results provided clear evidence for medium-sized visual-motor integration problems ($d = 0.69$), i.e. the ability to copy geometrical shapes, in a sample of 2132 VP/VLBW children derived from 32 studies using the Beery Visual-Motor Integration test. Visual-motor integration deficits were particularly present in boys as compared to girls, were positively associated with gestational age and intelligence, and persisted from childhood into adolescence.
Visual functioning of five-year-old VP/VLBW children was thoroughly investigated, including measures of oculomotor, visual sensory and visual perceptive functioning (chapter 3). This extensive examination revealed medium-sized dysfunctions in visual sensory functioning, as well as small to medium-sized dysfunctions in visual perceptive functioning. Specific visual dysfunctions were found in VP/VLBW children, including worse visual sensory functioning than term controls in terms of visual acuity, stereovision and the inferior visual field, and weaker visual perceptive functioning in terms of decreased sensitivity to visual coherence and visual-spatial perceptive dysfunctions. Visual sensory deficits were associated with a history of severe cranial ultrasound abnormalities and retinopathy of prematurity (ROP), but visual perceptive deficits were not associated with any of these neonatal morbidities. Notably, visual sensory and perceptive deficits were only weakly associated with each other, highlighting the fact that most VP/VLBW children with visual perceptive deficits remain unnoticed in routine screening of visual sensory functioning.¹

In addition to visual functioning, we investigated visual attention abilities of VP/VLBW children using newly developed and adapted measures of visual search and attention network functioning that minimized involvement of motor responses (chapter 4). Our visual search test minimized fine motor demands using a touchscreen. The systematic manipulation of task conditions in the attention network test (ANT) enabled us to control demands on non-relevant (motor) skills while obtaining indices of attention network efficiency. We found that, compared to term born children, VP/VLBW children showed small and medium-sized decreases in visual search performance and executive attention (i.e. processing conflicting information), respectively. VP/VLBW children showed longer search times and increased error rates during visual search, especially under high stimulus density conditions.

Taken together, the outcomes of the studies described in chapters 2 to 4 confirm the presence of visual sensory, visual perceptive, visual attention and visual-motor integration dysfunctions in VP/VLBW children. Specifically, our findings indicate mostly mild dysfunctions in visual acuity, visual field, binocularity, visual-spatial analysis, recognition under high stimulus density conditions and when processing conflicting information. Visual-motor integration deficits persist throughout childhood and into adolescence, consistent with difficulties in motor development.²

Based on the visual deficits that were found in the study described in chapter 3, a functional and empirically driven classification of CVI was investigated (chapter 5). Using this classification, CVI was almost four times more prevalent in VP/VLBW children than in controls. The concurrent validity of the CVI classification was confirmed by medium to large-sized increases in parent reported vision-related problems in children meeting
Table 1 Summary of the main findings of this thesis

<table>
<thead>
<tr>
<th>Chapter</th>
<th>Participants</th>
<th>Measures</th>
<th>Main findings</th>
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| 2       | Meta-analytic sample of 1478 children on visual perceptive functioning and 2132 children on visual-motor integration functioning. | Meta-analytic results of 16 studies on visual perceptive functioning (JLO, K-ABC Gestalt Closure, MVPT, NEPSY Arrows, TVPS-R) and 32 studies on visual-motor integration functioning (Beery VMI) | - Particularly visual-spatial perceptive dysfunction in VP/VLBW children  
- No effect of VP/VLBW on gestalt-closure  
- Inconsistent findings for visual perceptive measures providing composite scores  
- Consistent evidence for visual-motor integration dysfunction in VP/VLBW children  
- Visual-motor integration dysfunction is negatively associated with gestational age and is not associated with age at assessment |
| 3       | 116 VP/VLBW children 73 term born children | Oculomotor: eye position, motility, convergence, nystagmus, torticollis; Visual sensory: visual acuity, visual field, contrast, stereovision, color vision; Visual perceptive: DTVP-2, face recognition, static and moving coherence; Refractive status, WISC-III | - Visual sensory deficits of VP/VLBW children include visual acuity, inferior visual field and stereovision  
- Visual perceptive deficits of VP/VLBW children include static visual coherence and visual-spatial perception  
- No association between visual sensory and perceptive deficits  
- Moderately positive association between visual perceptive abilities and performance IQ |
| 4       | 108 VP/VLBW children 72 term born children | ANT, WISC-III, newly developed visual search test | - Worse visual search speed and accuracy in VP/VLBW children  
- Group by stimulus density interaction indicating specifically impaired visual search under high stimulus density conditions  
- Worse executive attention functioning in VP/VLBW children  
- No effect of VP/VLBW on alerting and orienting attention  
- Weak and positive association between attention abilities and full scale IQ |

### Table 1 (continued)

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<th>Chapter</th>
<th>Participants</th>
<th>Measures</th>
<th>Main findings</th>
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| 5       | 105 VP/VLBW children  67 term born children                                 | Oculomotor, visual sensory, visual perceptive measures (detailed above, chapter 3), visual attention measures (detailed above, chapter 4); CSBQ, SDQ, WISC-III, CVI questionnaire | • Empirical CVI classification is almost four times more prevalent in VP/VLBW children (24%) than in term controls (7%)  
• CVI-status positively associated with vision-related problems as indicated by CVI questionnaire  
• CVI-status positively associated with behavioral and social difficulties as indicated by SDQ and CSBQ  
• No effects of VP/VLBW without CVI on CVI questionnaire, SDQ and CSBQ  
• Stepwise effect of CVI and VP/VLBW on performance IQ: VP/VLBW with CVI < VP/VLBW without CVI < term control  
• No effect of CVI-status on use of therapeutic services or visual rehabilitation |
| 6       | 106 VP/VLBW children                                                       | Oculomotor, visual sensory, visual perceptive measures (detailed above, chapter 3), visual attention measures (detailed above, chapter 4); Beery VMI, M-ABC, neurological examination according to Touwen | • Impaired motor functioning in 23-36% of VP/VLBW children  
• Weak negatively association between oculomotor and visual-motor integration deficits on motor functioning  
• Moderate negatively association between abnormal neurological status on motor functioning |

Note. CVI: cerebral visual impairment  
Visual imprints of very preterm birth.

Criteria for our definition of CVI. No differences in vision-related problems were found between VP/VLBW and term born children without CVI. In addition, analyses of attention and intellectual functioning indicated worse selective attention and performance IQ in VP/VLBW children with CVI. Similar to parent reported vision-related problems, medium to large-sized behavioral and social difficulties were also specifically present in VP/VLBW children with CVI. Interestingly, the difficulties associated with CVI-status did not translate to referrals to therapeutic services or visual rehabilitation.

Visual deficits potentially underlying motor functioning of VP/VLBW children were investigated by analyzing the predictive value of oculomotor, visual sensory and visual perceptive deficits, as well as deficits in visual attention and visual-motor integration functioning on motor performance (chapter 6). We confirmed motor problems in VP/VLBW children. Oculomotor and visual-motor integration deficits were weakly predictive of motor functioning. Visual perceptive deficits were weakly associated with aiming and catching ability. In contrast to the weak associations between these visual deficits and motor functioning, abnormal neurological status was moderately associated with motor performance, suggesting that abnormalities in brain development may be more fundamental for the difficulties in motor performance of VP/VLBW children, than abnormalities in visual functioning.

Taken together, the findings described in and chapter 5 and chapter 6 suggest that visual deficits in VP/VLBW children are differentially associated with intellectual, behavioral and motor functioning. Whereas visual deficits, particularly those covered by the CVI classification, were substantially associated with lower performance IQ and difficulties in social and behavioral functioning, visual deficits were not or only weakly related to motor performance of VP/VLBW children. In addition, the CVI classification study (chapter 5) shows that CVI is associated with vision-related as well as non-visual behavioral difficulties in VP/VLBW children, thereby highlighting the possibility that CVI acts as a sensitive indicator of these behavioral difficulties and that the questionnaires for vision-related problems, and social and behavioral functioning cover overlapping aspects of the behavioral outcome of VP/VLBW children.
GENERAL DISCUSSION

Visual functioning
Our meta-analysis (chapter 2) demonstrated difficulties in visual perceptive and visual-motor integration functioning of VP/VLBW children. These difficulties add to the existing meta-analytic evidence of problems in motor, (neuro)cognitive, behavioral, language and academic functioning in VP/VLBW children. Impaired visual perceptive and visual-motor integration functioning was also confirmed in our own data (chapter 3 and chapter 6), showing that VP/VLBW children display a specific profile of visual dysfunctions across the domains of oculomotor, visual sensory and visual perceptive functioning (chapter 3). While oculomotor and visual sensory dysfunctions have been frequently and consistently reported, existing findings on visual perceptive outcome are less consistent. Our systematic review identified only few studies reporting on visual perceptive outcome. Nonetheless, results of both our meta-analysis and our own data converged in demonstrating impaired visual-spatial perceptive functioning in VP/VLBW children.

We extended the profile of visual functioning with measures of visual attention (chapter 4). Attention is considered a core factor underlying the regulation of human behaviour and neurocognitive functioning and is a crucial prerequisite for development. Difficulties in attention functioning have recently received enormous interest as explanatory factor for the adverse developmental outcome of VP/VLBW children. For instance, processing speed and variability of processing speed have been found to account for attention problems as well as problems in academic attainment. Using child-friendly adaptations of firmly established paradigms measuring attention functioning, we found specific deficiencies in visual search under high stimulus density conditions. In addition, the ANT that differentiated between alerting, orienting and executive components of attention, revealed a specific deficit in executive attention in VP/VLBW children, consistent with other studies using the ANT.

Specific visual dysfunctions in VP/VLBW children are present across a range of oculomotor, visual sensory and visual perceptive abilities, as well as in aspects of attention functioning. Remarkably, we found that minimizing additional task demands revealed more specific and less pronounced attention problems, as compared to existing evidence, suggesting that earlier studies using motor-driven attention tests might have overestimated attention deficits in VP/VLBW children. Our visual search test also observed smaller differences between VP/VLBW and term children than usually found using conventional paper and pencil search tests. Smaller differences between VP/VLBW and term born children using tests that minimize motor demands have also been found in a study on executive functioning. On the one hand, these insights stress the need for...
paradigms to adequately evaluate developmental outcomes of VP/VLBW children. On the other hand, these findings might indicate that VP/VLBW children particularly struggle when integrating multiple abilities, as is the case in many activities in daily life.

Dorsal stream vulnerability
A large body of fundamental research into the neural mechanisms of vision has contributed to firmly grounded models aiding our understanding of vision. New insights continuously contribute to these models, and have helped understanding the disorders of vision. For instance, the long standing distinction between the “dorsal” and “ventral” cerebral streams of visual information processing (referring to action-related visual abilities and visual abilities related to recognition, respectively) has led to the adoption of the “dorsal stream vulnerability” hypothesis, that is currently thought to account for the visual deficits observed in VP/VLBW children. This model argues that visual as well as attention and visual-motor integration functions pertaining to occipital-parietal-prefrontal networks (i.e. dorsal visual stream) are particularly affected in VP/VLBW children. The findings of our meta-analysis as well as our own data showed predominantly visual-spatial perceptive and visual-motor integration dysfunctions, thereby converging with the idea of dorsal stream vulnerability.

Several studies have employed newly developed paradigms to measure specific aspects of visual perceptive functioning and to elucidate the fundamental deficits underlying visual perceptive problems in VP/VLBW children. For instance, research groups have investigated visual perceptive deficits in these children using paradigms specifically assessing motion sensitivity, motion based recognition, and perception of visual-spatial configuration. Interestingly, these studies indicated deficient visual-spatial or motion-related aspects of perception, converging with the dorsal stream vulnerability hypothesis. In our sample, VP/VLBW children performed worse on a static visual coherence test (i.e. perception of global form), but did not differ from term controls in perceiving moving visual coherence (i.e. perception of global motion). This finding might be interpreted as indicative of ventral stream impairment, since motion and static coherence sensitivity have been suggested to act as measures of dorsal and ventral stream functioning, respectively. However, functional magnetic resonance imaging (fMRI) and event related potential (ERP) studies have shown that these measures, despite relying on independent neural circuitries, do not map one to one onto dorsal/ventral segregated neural circuitries. Furthermore, global motion sensitivity shows a more variable developmental course in early childhood, as compared to global form sensitivity. This increased variability might have precluded group differences in our study sample of relatively young children. In addition, other measures of ventral stream functioning such as recognition of faces and objects indicated no difficulties in our sample of VP/VLBW
children, suggesting that it would be inappropriate to attribute the group difference on static coherence sensitivity in our sample to affected ventral stream functioning. Moreover, several aspects of both the nature of visual perceptive dysfunctions in VP/VLBW children as well as their neural underpinnings are awaiting investigation in future studies. Interestingly, one study using fMRI has revealed altered activation of frontal-parietal-occipital networks during encoding of visual stimuli in VP/VLBW children while task performance did not differ from performance of controls, thereby suggesting less efficient processing of visual information. The few existing neuroimaging studies addressing the dorsal stream vulnerability hypothesis of VP/VLBW children, however, do not tap into the role of specific dorsal and other tracts of the extended neural network underlying visual functioning and may be confounded by required manual abilities. Future studies combining advanced neuroimaging techniques with measures targeting selective aspects of visual perceptive functioning are warranted to further progress in validating the dorsal stream vulnerability hypothesis.

Associations with intellectual functioning

Differences in intellectual functioning between VP/VLBW and term born children are among the most frequently reported findings. We explored the associations between deficits in visual as well as attention functioning on the one hand, and intellectual functioning on the other hand. We found a specific relationship between visual deficits and IQ, i.e. visual perceptive deficits were moderately and inversely associated with performance IQ. In contrast, visual sensory as well as perceptive deficits were only weakly associated with verbal IQ (chapter 3). Similarly, VP/VLBW children classified with CVI had lower performance IQ, but not verbal IQ than those without CVI (chapter 5). Since visual sensory deficits were not associated with performance IQ, it seems unlikely that the association between CVI and performance IQ originated from deteriorated visibility of the performance IQ testing materials. Furthermore, deficits in visual attention were moderately and inversely associated with full scale IQ (chapter 4). These findings add to the emerging insight that the well-established differences in intellectual functioning between very preterm and term born children might result from a cascade of more fundamental deficits in neurocognitive functioning. Further insights into the neurocognitive deficits underlying IQ differences between VP/VLBW children and controls might provide fruitful opportunities to interventions, for instance by targeting underlying executive dysfunctions.

Neural correlates

We found that unfavorable events during the neonatal period were associated with visual deficits, reflecting underlying brain damage. Visual sensory deficits were associated with retinopathy of prematurity (ROP) and severe cranial ultrasound abnormalities, in contrast to visual perceptive deficits that were only associated with a history of ROP (chapter 3).
Visual attention deficits were not associated with neonatal morbidities (chapter 4). Our CVI classification, comprising most of the cases with visual sensory as well as perceptive deficits, was particularly associated with a complicated neonatal history, including lower birth weight, respiratory support, oxygen dependence and septic events (chapter 5). In our meta-analysis, visual-motor integration ability was inversely associated with gestational age (chapter 2). Such a relationship was not found in individual studies,\textsuperscript{45,46} suggesting that this association becomes only evident if a broad range of GA is included and might be mediated by complicated neonatal histories and resultant minor neurological dysfunction pertaining to extremely preterm birth.\textsuperscript{47,48} Overall, respiratory and infectious events that are known to hamper neural migration, axonal outgrowth and myelination, are risk factors for brain damage, as reflected by abnormal ultrasound findings in our sample,\textsuperscript{49} and are associated with the visual deficits that we found. Besides disturbances in brain development, these respiratory and infectious events also impinge on retinal vasoproliferation, thereby causing the risk of ROP,\textsuperscript{50} and thus affecting both peripheral and central parts of the visual system.\textsuperscript{51}

Several studies have begun to unravel the neural correlates of visual dysfunctions in VP/VLBW children using advanced techniques such as diffusion tensor imaging (DTI). Studies using DTI have highlighted the role of integrity of the optic tract in visual functioning. Better integrity of optic radiation tracts in very preterm infants is associated with better visual fixation ability,\textsuperscript{52,53} oculomotor functioning and with higher visual acuity.\textsuperscript{53,54} By seven years of age, increased optic radiation integrity is associated with higher visual acuity and a decreased likelihood of visual perceptive deficits,\textsuperscript{55} whereas in very preterm adolescents callosal and frontal white matter integrity is positively associated with visual acuity.\textsuperscript{56} So far, studies have mainly focused on visual sensory functioning associated with white matter integrity. Given the wide range of tracts associated visual sensory abilities, further insight into the causality of such relationships as well as potentially mediating factors is required.

Knowledge on the neural correlates of visual dysfunctions of VP/VLBW children is still in its infancy. Our findings indicate that visual deficits are most prominent in the most vulnerable subgroup of VP/VLBW children that survived the critical neonatal period. This finding is consistent with results from early studies on visual deficits in children suffering from hypoxic-ischemic disease.\textsuperscript{57} Future neuroimaging studies may provide further insights into the neural correlates of visual deficits including CVI in VP/VLBW children, thereby also advancing the debate on the role of affected dorsal and/or ventral steam functioning in these children.
Definition of CVI in VP/VLBW children
The existing terminology of CVI is not as consistent as one could wish for, and is subject to ongoing debate.\(^{58}\) Defining features of CVI have been described across different levels of human functioning, including anatomical, functional and behavioral levels.\(^{57-66}\) This diversity has not only given rise to an increased awareness of CVI and accompanying demands on clinical care, but is also accompanied by a great diversity of sometimes contradicting views on CVI. For instance, no agreement exists in terms of the use of cerebral imaging measures, tests to assess (cerebral) visual functioning, or the use of behavioral screening questionnaires to diagnose CVI. A commonly accepted conceptual framework and an accompanying diagnostic guideline are warranted to progress towards further understanding of CVI.\(^{59,67}\) The WHO International Classification of Functioning (ICF) model describes a conceptual framework for the taxonomy of human functional disability, including structural (anatomy), functional, and activity/participation levels of functioning, which should organize the diversity of ideas on CVI.\(^{68,69}\) In terms of the WHO-ICF model, our CVI classification defines CVI at the functional level. The conventional definition of CVI emphasizes the anatomical (structural) level, whereas questionnaire-based procedures to detect CVI\(^{62,70,71}\) primarily address the activity/participation level of functioning.

In this thesis, CVI was classified using a broad definition based on functional-empirical criteria for visual deficits. This definition incorporated recent insights indicating processing of visual information in the visual system from the retinal neural layers onwards, and showing that eventual “ocular” conditions such as amblyopia and stereovision deficits are accompanied by affected processing of visual information.\(^{31,72}\) Our definition is more cautious in excluding visual deficits from CVI, contrasting the conventional idea that CVI is due to brain damage posterior to the optic chiasm.\(^{60,63,73}\) Consequently, our definition of CVI also included deficits in oculomotor and visual sensory functioning for cases in which these deficits were not due to refractive error. Notably, oculomotor deficits in our children with CVI were always accompanied by other visual deficits. Abnormalities in eye position or convergence alone were not considered CVI in our sample.

Using this definition of CVI, we found an almost four-fold increase of CVI in VP/VLBW children, compared to term born peers. Our results indicated that the functional CVI classification showed good agreement with behavioral aspects of CVI (activity/participation level), as indicated by medium to large-sized associations between the CVI classification and parent reported vision-related problems in daily life (chapter 5). Surprisingly, difficulties at activity/participation level were not accompanied by increased demands on therapeutic services including visual rehabilitation. Referrals to any therapeutic service were based on multidisciplinary case-wise consultation, suggesting that CVI was not the most severe or most prominent disability that required remediation at the relatively young age of our VP/VLBW sample. Furthermore, our results showed that
VP/VLBW children with CVI displayed worse performance IQ as well as difficulties in social and behavioral functioning (chapter 5). In contrast, we found only weak associations between the results of our extensive visual assessments and motor performance (chapter 6), suggesting differential rather than overlapping characteristics and pathophysiology for CVI and developmental coordination disorder (DCD).

The good agreement between our CVI classification and the parent reported vision-related problems is supportive of the validity of our definition of CVI. VP/VLBW children with CVI were, however, not more often referred to therapeutic services or visual rehabilitation than those without CVI. These findings seem to contradict earlier studies that have identified preterm birth as major risk factor for CVI in clinical samples of children with CVI. Differences between these studies and our cohort study are most likely due to overrepresentation of high risk preterm children in clinical samples, in contrast to our representative birth cohort sample. In addition, the severity of CVI might have decreased over the past decades, consistent with decreased frequency and severity of white matter abnormalities. Nevertheless, our findings leave the possibility that CVI is more severe or occurs more often in a subgroup of high risk VP/VLBW children. Our CVI classification also successfully differentiated between VP/VLBW children with and without a wider range of adverse developmental outcomes, including lower performance IQ and difficulties in social and behavioral functioning. Another study that defined CVI in VP/VLBW children using a CVI questionnaire also reported that specifically the subgroup of VP/VLBW children with CVI showed difficulties in a wider range of attention and visual perceptive abilities. These findings illustrate that CVI coincides with the wider spectrum of neurodevelopmental dysfunctions in VP/VLBW children and raise doubts about the differential validity of the concept of CVI. In addition, our findings raise doubts about the specificity of behavioral CVI assessment scales.

Our findings have clearly indicated that a range of visual dysfunctions, accumulated in the CVI classification, are present in addition to frequently reported adverse outcomes in intellectual and behavioral functioning in VP/VLBW children. These comorbid conditions converge with the results of follow-up research over the past decade that has shown that VP/VLBW children display a heterogeneous picture of neurodevelopmental dysfunctions across multiple domains of functioning typically referred to as “high frequency of low severity” comorbid dysfunctions. On the one hand, or findings indicate that our CVI classification might act as a marker targeting a subgroup of VP/VLBW children at risk for a wider range of adverse developmental outcome. On the other hand, the differential validity of the CVI concept seems very limited, thereby raising doubts about its utility in terms of a visual condition requiring remediation from visual rehabilitation services.
Future perspectives of CVI in VP/VLBW children

Several important topics are awaiting future studies, including unresolved issues on the definition of CVI and advanced diagnostic procedures that might ultimately allow targeted interventions. Most importantly, the issue of comorbidity warrants further clarification to increase the differential validity of CVI, thereby disentangling CVI from other developmental disorders. Such an advanced definition of CVI may differentiate between those children with prominent cerebral visual disorders requiring visual rehabilitation, and children with milder visual impairments in addition to other neurodevelopmental difficulties. In terms of the WHO-ICF model, advances at the structural, functional as well as the activity/participation level may benefit an advanced definition of CVI. At the structural level, currently, differentiating between optical and neural causes of visual deficits seems most appropriate, consistent with recent insights into retinal involvement in processing of visual information, and since neuroimaging techniques do not allow accurate differentiation between visual and non-visual cerebral structures. At the functional level, differentiating between visual and non-visual neurocognitive deficits is highly important to distinguish CVI from other neurocognitive dysfunctions. At the activity/participation level, valid questionnaires are a prerequisite to meaningfully differentiate between behavioral signs of CVI and the wide range of behavioral and social difficulties pertaining to psychopathology. Confirmatory evidence for a visual disorder at each of these levels may be indicative of a case of specific CVI, i.e. damage to the neural visual system, more severe deficits in visual functioning as compared to other domains of functioning, and impaired visual functioning in daily life compared to other aspects of behavioral functioning.

Furthermore, possibly milder forms of CVI may frequently co-occur with other neurodevelopmental problems, such as the case in our sample, and consistent with the pattern of high frequency of low severity co-morbidities of VP/VLBW children. In addition, abnormalities in visual functioning occur in a range of developmental disorders, including preterm birth, Williams syndrome, hemiplegia and autism, due to presumed underlying dorsal stream dysfunction that is thought common to these disorders. Such cases strikingly highlight the need that adequate differentiation between visual and non-visual causes of behavioral difficulties should guide diagnostic decision-making and subsequent interventions, to avoid false positive classifications and treatment of CVI. For instance, inattention or focusing on details instead of global percepts can be accounted for by symptoms of Attention Deficit/Hyperactivity Disorder and autism spectrum disorder, respectively, that are both frequently present in VP/VLBW children. On the one hand, remediation of the visual difficulties in these conditions appears of minor importance, given their presence among other dysfunctions that are more fundamental to the disorder and more urgently requiring remediation. On the other hand, many VP/VLBW children present with multiple but subtle dysfunctions, that are not
captured by current criteria of developmental disorders. Those children might require tailor-made interventions adjusting for their specific difficulties in visual and other domains of functioning, thereby contributing to an integrated and transdisciplinary intervention. Future studies are warranted to evaluate advances in diagnostic criteria for CVI as well as to evaluate the additional efficacy of visual interventions in cases with minor visual difficulties. In addition, advances in such studies might benefit from further insights into the fundamental question on the causality of the relationship between CVI and associated adverse developmental outcomes.

Our findings have some, albeit limited, implications. The weak association between visual sensory and visual perceptive deficits that we found highlights that visual screening procedures that usually rely on visual sensory measures do not detect VP/VLBW children with visual perceptive dysfunctions. Addition of visual perceptive measures to follow-up programs of VP/VLBW children should be considered to evaluate a broader range of visual functioning, and will likely also identify VP/VLBW children at risk for other adverse neurodevelopmental outcomes. Furthermore, acceptance criteria for visual rehabilitation usually adhere to the WHO criteria for visual sensory impairment, thereby excluding children with visual perceptive deficits. Should the acceptance criteria for visual rehabilitation be extended to also include CVI, more stringent diagnostic criteria are highly recommended to avoid false positive CVI classification and to adequately indicate visual rehabilitation needs.

Opportunities for targeted interventions of CVI are awaiting further validation of the concept of CVI. Since our results have shown that CVI in a representative sample of VP/VLBW children does not appear to represent a substantial visual disorder requiring remediation, interventions should only be cautiously indicated. Currently, intervention programs for children with CVI mainly consist of best practices. Interestingly, the post-discharge intervention that was performed in the sample of our study showed a long-term small-sized beneficial effect on visual-motor integration functioning, thereby suggesting that an early and non-visual intervention might aid children with visual-motor integration dysfunctions. Since this intervention was not found beneficial to any of the visual and attention measures in our study, the effects might be specifically found in abilities requiring integration of multiple aspects of functioning. Future interventions for CVI should target specific deficits underlying the visual disorder, thereby aiming at improving visual functioning and concomitant activities/participation in society.

Strengths and limitations
The studies presented in this thesis have their strengths as well as their limitations. The results of our studies are derived from a large and representative sample of VP/VLBW children, in terms of the incidence of ROP, PVL, IVH and severe ultrasound...
abnormalities.\textsuperscript{91-94} Additionally recruited term born controls of a similar age range and socio-economic background, allowed sensible comparison between VP/VLBW and term born children in order to investigate the effects of VP birth/VLBW on visual functioning. Another important strength is that visual development of VP/VLBW children was evaluated at multiple levels of visual functioning that ranged from elementary oculomotor to advanced visual perceptive abilities. In addition, evaluation of visual outcome was complemented with assessment of attention, visual-motor integration, motor, intellectual and behavioral functioning, allowing us to study repercussions of visual deficits on motor, intellectual and behavioral outcome. Uniform criteria to define deficient performance were consistently applied across all measures used. Furthermore, assessments comprised tests that are commonly used in clinical settings, supporting the clinical generalizability of our findings.

The studies presented in this thesis also have some limitations. All VP/VLBW children initially participated in a trial on a post-discharge intervention,\textsuperscript{95} that might have interfered with our results. This intervention, however, was not specifically directed at improving visual development, and in all analyses potential effects of the intervention have been investigated. No meaningful effects of the intervention on any of our measures have been found, except for beneficial effects on performance IQ and visual-motor integration functioning.\textsuperscript{90} Analyses including these measures have been adjusted for intervention status. Another limitation, inevitable in follow-up research, is the dropout of participants of earlier follow-up moments. Of the 176 children participating in the original trial, 160 were still available for follow-up at 5.5 years of age, of whom 136 (77\%) agreed to participate. Participating and non-participating children did not differ in terms of neonatal and socio-economic characteristics at discharge, except that more children from single-parent households and non-Dutch speaking families were lost to follow-up, consistent with other studies.\textsuperscript{96} Another limitation is that our orthoptic assessments relied on non-cycloplegic video refraction, which may underestimate refractive error.\textsuperscript{97} Instead, children were tested with their habitual correction, if they had any, and in the analyses, refractive error was defined by two measures: 1) children wearing prescription glasses, and 2) children suspected of refractive error at the time of our assessments as judged by the orthoptists based on the complete visual sensory assessment (e.g. because of suboptimal performance on visual acuity tests, lower acuity in one eye, absent stereovision, strabismus or insufficient convergence). Subsequently, both measures of refractive error were included in the analyses and all results remained essentially unchanged when corrected for this potential bias. Furthermore, no MRI measures from term age or age at follow-up were available that would have enabled us to study the neural correlates of CVI in detail. Finally, all studies have been performed in the same sample of VP/VLBW children, which facilitates the integration of results from the individual studies, but also might have caused bias related to idiosyncratic characteristics
of sample studied. Our findings need cross validation in other studies to support their validity.

Concluding remarks

Our findings indicate a specific profile of oculomotor, visual sensory as well as perceptive dysfunctions in VP/VLBW children, converging with much of the existing evidence.\textsuperscript{9-15,98-101}

Our findings extend this evidence by providing and integrative picture of these aspects of visual functioning, as well as additional visual attention and visual-motor integration functioning. Visual deficits, ultimately accumulating in the functional and empirically driven classification of CVI, were particularly associated with adverse non-verbal intellectual and behavioral functioning, but were only weakly associated with the prominent motor difficulties of VP/VLBW children. Our findings also raise doubts about the differential validity of the concept of CVI, highlighting important issues in advancing the conceptualization of CVI, and for future studies aiming at understanding visual development of VP/VLBW children.

\begin{thebibliography}{99}
\item Mulder H, Pitchford NJ, Marlow N. Processing speed and working memory
Summary and general discussion

Our findings need cross-validation in other studies to support their validity.

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