This study was designed to increase the knowledge on neuropsychological diagnosis of cerebral visual dysfunction ('cerebral visual impairment') in children with brain damage or an increased risk of brain damage, as well as to evaluate available diagnostic methods. We focused on motion perception and other dorsal stream functions and on the age group 4 to 7 years.

In **Chapter 1**, a general introduction to the theme is given, with information on current barriers to early diagnosis and intervention by specialised low vision centres in the Netherlands. Groups considered at risk are children with cerebral palsy and/or intellectual disability, and prematurely born children. Factors hampering epidemiological research as a basis for evidence-based diagnostic procedures and habilitation are elucidated, the lack of easily applicable and valid quantitative diagnostic tests being one of them. We decided to specifically address cerebral functions associated with the dorsal stream of the visual system: object recognition under suboptimal conditions, motion perception, visuomotor abilities and visual attention.

In **Chapter 2**, we focus on early recognition of children at risk for cerebral visual problems from the perspective of different levels in the diagnostic chain: youth healthcare, ophthalmology, and expert low vision centre. We assessed abnormal crowding (difficulties handling complex visual information) in 60 typically developing school children, 21 typically developing children with ocular abnormalities, and 26 children with indications of brain damage, using Teller Acuity Cards-II and Cambridge Crowding Cards. The aim was to evaluate whether the crowding ratio and the ratio between grating acuity and optotype acuity differentiate better than visual acuity alone between children without neurological and ocular abnormalities, children with ocular disorders only, and children with (potential) brain damage.

For youth healthcare, subnormal crowded acuity had the best sensitivity (76%) and specificity (70%), and for ophthalmology and low vision centres, the crowding ratio, with a sensitivity of 67% and a specificity of 79 and 86%, respectively.

Proportions of weak performers on cerebral visual function tests did not significantly differ between groups with and without abnormal crowding.

We conclude that crowding and perception problems seem to be independent but co-occurring impairments, implying that crowding cannot be applied directly to screen for cerebral visual dysfunction. Youth health professionals best continue screening with crowded acuity, whereas ophthalmologists and low vision experts best add the crowding ratio to their routine diagnostics,

to distinguish children at risk for visual dysfunction in the context of brain damage from children with ocular pathology.

Chapter 3 is a short introduction into the concept of motion perception, including current insight into its representation in the brain and different aspects of motion perception: global or coherent motion perception, perception of complex motions, perception of biological motion, and perception of motion-defined forms. Quantitative methods to measure motion perception are usually based on moving dots: the random dot kinematogram (RDK) is used for perception of global or coherent motion, motion direction and motion-defined form. For biological motion, point-light figures are mostly applied. The advantage of such tasks above observational tasks is, that they provide a threshold value. A variety of computerised tasks have been developed by investigators around the world. However, at this stage, most have only been applied in research settings.

Chapter 4 is a systematic review of the scientific literature on computerised motion perception tasks, with the aim to judge their current applicability in clinical practice for children. We focussed on confounding risks, task aspects, thresholds used, sample limits or cut-off values, and performance of risk groups compared to typically developing children. Twenty-six articles were included, all cross-sectional, of which 22 focussed on a single motion perception aspect. Global motion has been studied most intensively, whereas smaller numbers of studies focussed on motion-defined form and biological motion.

The confounding risk was low in 6, moderate in 10 and high in 10 of these studies. In eight out of 16 studies with a low or moderate confounding risk, some kind of sample limit or cut-off value was used. There is a wide variety in task characteristics, and confidence intervals for normal limits are wide as a result of small age-groups. Combining outcomes of studies using similar tasks, we observed developmental trends for global motion and motion-defined form.

Eight studies addressed performance of patient groups (mean group size 21, range 8-93) compared to typically developing children. Taking confidence intervals for normal limits into account, there is some evidence for an increased risk of abnormal performance in prematurely born children, children with autism and children with amblyopia.

We conclude that so far, computerised motion perception tasks can be used in clinical practice as observational instruments with quantifiable outcomes, but because of unreliable normal limits, weak performance cannot be identified reliably.

Chapter 5 addresses the relation between chronological age versus developmental age and the outcomes of four motion perception tasks. We administered a global motion task consisting of a random dot kinematogram (RDK) with a variable proportion of dots coherently oscillating in a horizontal direction, a motion-defined form task consisting of objects hidden in an RDK, a biological motion task consisting of a human dot figure walking and a motion speed task consisting of two identical cars filled with dots moving with different speed. We investigated these tasks in 49 children with indications of brain damage and 60 out of 119 controls. A second aim was to construct and evaluate normal limits for motion perception, to be used in clinical practice.

In children with brain damage, all aspects of motion perception were related to developmental age only. In controls, no significant difference in motion perception performance was found applying developmental or chronological age. We conclude that in children with brain damage, developmental age should be used as input for the norm tables, to avoid overestimation of motion perception problems.

Data of all 119 controls were used to construct preliminary normal limits, as well as developmental trends, based on percentile scores of different chronological age groups. A bottom effect for the biological motion task was found. Therefore, clinical evaluation on this task is not useful. Suggestions for careful clinical application of the outcomes of the other motion perception tasks are given.

Chapter 6 is the report of an experimental study into motion perception of 46 children with indications of brain damage with the aim to investigate which aspects of motion perception should be addressed, i.e. whether children with brain damage have isolated or multiple motion perception weaknesses. We also evaluated the clinical impact of chronological age and developmental age as reference level when interpreting motion perception performances by applying the above preliminary limits for normal performance (Chapter 5). We evaluated results of a global motion task, of motion-defined task and a motion speed task. A significantly increased risk of abnormal performance was specifically found for global motion and motion-defined form. We primarily found that specific and not multiple aspects of motion perception were affected and the use of chronological age as reference level increases the risk of overdiagnosis significantly.

Chapter 7 describes a study into different dorsal stream functions. It was specifically aimed at the question whether children with indications of brain

damage and problems with object recognition under suboptimal conditions, have a general or a specific dorsal stream dysfunction. Object recognition in sub-optimal conditions was assessed with five computerised subtasks of the L94. Motion perception was assessed with computerised motion perception tasks for global motion, motion-defined form, biological motion, and motion speed (see Chapter 5). Visuoconstructive skills were assessed with the Beery VMI and the subtest mosaics of the SON-R, and visual attention with a computerised visual search task. Missing normal limits were based on outcomes in 60 typically developing children aged 4-7 years. Forty-eight children at risk for visual perception problems were divided in a group with normal and a group with abnormal object recognition (score below 5th percentile). A general dorsal stream dysfunction was considered present if a majority of participants with object recognition problems would perform weak (score below 10th percentile) on at least two additional dorsal stream functions.

Compared to participants with normal object recognition, participants with object recognition problems performed significantly more often weak on motion perception and visual attention, but not on visuoconstructive skills. A minority had a general dorsal stream dysfunction. We conclude that in children with object recognition problems, dorsal stream dysfunctions seem to be rather specific than general. Therefore, multiple aspects and functions should be assessed in neuropsychological assessment of children at risk.

The used visual search task was first developed in 2002 by master thesis students at Leuven Catholic University. In the Appendix, its procedure is described, as well as our construction of normal limits in a group of 60 typically developing school children, aged 4-7 years, divided in three age groups.

Chapter 8 is a description of a paradigm using a different, innovative diagnostic approach. Its development was initiated by a collaboration with the Neuroscience department, Erasmus MC. The rationale for this collaboration was the urgent need of objective quantitative motion perception tests applicable to children aged younger than 4 years and children as well as adults with severe intellectual disabilities. Based on remotely tracking of reflexive eye movements towards specific visual stimuli, shown on a computer screen, objective outcomes can be obtained in a very short time.

The aim of the current study was, to quantify processing of different types of coherent motion in terms of ocular motor fixation times in a group of 188 typically developing children (age 0-13 years), divided into two age groups (0-3+ and 4-11+ years). Motion coherence was applied in three different types of random dot kinematograms (RDK): vertical (RDK1) and diagonal (RDK2)

motion, and expansion (RDK3). Orienting eye movements were quantified measuring reaction time to fixation (RTF).

RTF was significantly prolonged in the young group compared to the older group, whereas in the older group, RTF was significantly affected by the type of RDK shown.

The results suggest that based on ocular motor responses, differences in processing of types of coherent motion can be revealed. This result has encouraged us to further develop and evaluate different types of visual stimuli.

Chapter 9 is again a description of an eye tracker study. This time, the focus was not on assessment of visually-guided responses, but on assessment of different fixation strategies during a Gestalt perception task. Such task assesses the ability to visualize a complete whole when presented incomplete information or a partial picture, a so-called Gestalt item. To our knowledge, this is one of the first studies on Gestalt perception in visually impaired children with a special focus on (sustained) visual attention. The database of a longitudinal eye tracking study consisted of 72 patients/clients of Royal Dutch Visio who underwent the Gestalt closure test. Digitised Gestalt items were shown one-by-one on a monitor with an integrated eye tracker to test the performance and to quantify the number of fixations and the mean and total fixation duration. The children were divided in three different groups: ocular visual impairments (OVI; n = 38), ocular and cerebral visual impairment (OCVI; n = 14) or cerebral visual impairments (CVI; n = 20). Children with visual impairments performed more often weak than age-matched American controls. Differences remained significant even after controlling for differences in cognitive level. Children with brain damage performed significant worse on the animate items than the group without brain damage. The data collected on orienting attention revealed that this performance in the CVI children could not be attributed to a lack of effort.

Chapter 10 is a general discussion of all findings and their implications for clinical practice and research. Most important outcomes are, that in children with (suspected) brain damage:

1. the crowding ratio can be used as a detection instrument for possible brain dysfunction in the population that is referred for ophthalmological or specialised low vision assessment, but is insufficiently effective for screening in the unselected children's population;
2. results of motion perception tasks should be evaluated against developmental age and not chronological age;

3. problems are specifically found for global motion and motion-defined form perception;
4. motion speed problems are scarce, but motion speed discrimination is a complex task and cognitive limitation hampers understanding of the test;
5. biological motion tests are too difficult for this developmental age group and/or its' validity is questionable;
6. other dorsal stream problems (object recognition, visual attention, visuo-contructive functioning) are more often isolated than simultaneous present;
7. object recognition problems are associated with weak motion perception and weak visual attention, but not with weak visuoconstructive functioning;
8. the performances on Gestalt perception are weak compared to the children without brain damage. Specifically recognising the animate items seems impaired.

Main recommendations for improvement of clinical practice are:

1. Addition of crowding assessment to routine orthoptic diagnostics of children in (paediatric) ophthalmology clinics;
2. Addition of crowding assessment to routine orthoptic intake assessments in specialist low vision services; and
3. addition of 'confirmed brain damage' or 'explicit risk of brain damage' to the current Dutch eligibility requirements for specialised diagnostic assessment in low vision services.

These measures will improve detection and expert diagnosis of children with cerebral visual dysfunction.

Most of the quantitative neuropsychological tests used appear applicable and valid. The eye tracker study presented in Chapter 8 was part of the evaluation and validation studies that were conducted by the Neuroscience department of Erasmus MC and Royal Dutch Visio. This has recently led to implementation of eye tracking within low vision centres. In Chapter 9, the joining of forces between the departments of Intellectual Disability Medicine and Neuroscience, Erasmus MC, took a new turn in developing eye tracking paradigms with a special focus on testing neuropsychological aspects.

Before these new paradigms can be added to routine diagnostic assessment in low vision services, normal limits have to be evaluated in larger samples, so this is our most relevant recommendation for collaborative (international) research. To date, together with the Vestibular and Ocular Motor Research Group

of the dept. Neuroscience, Erasmus MC, the dept. of Paediatrics, Subdivision of Neonatology and Pediatric Intensive Care, Erasmus MC – Sophia Children's Hospital and Royal Dutch Visio new future paradigms and applications are designed, evaluated and validated.