Curriculum Vitae

Fleur Heleen Boot werd geboren op 11 september 1981 in Redhill (Engeland). In 1999 behaalde zij haar VWO diploma aan het Geert Grote College te Deventer. Net een week 18 jaar, vertrok Fleur als "backpacker" voor 9 maanden naar Australië en Nieuw Zeeland. Terug in Nederland heeft zij een jaar life, science & technology gestudeerd aan de Technische Universiteit Delft.
In 2001 is Fleur begonnen met haar studie geneeskunde aan de Erasmus Universiteit te Rotterdam. Haar keuze coschap chirurgie heeft zij in Ifakara, Tanzania gedaan en haar afstudeeronderzoek KNO in Manchester, Engeland. Na haar artsexamen op 19 december 2008, bleef de vraag voor haar; "welke weg sla ik in"? Een half jaar van onzekerheid en zelfonderzoek volgde. Het resulteerde in de wens en mogelijkheid om promotie onderzoek te doen aan het Erasmus MC te Rotterdam bij de afdeling Neurowetenschappen en Geneeskunde voor Verstandelijk Gehandicapten en opgeleid te worden als AVG (arts voor verstandelijk gehandicapten).
Momenteel werkt Fleur als basisarts bij Tragel Zorg in Clinge en zal in februari 2013 beginnen met haar opleiding. Om haar onderzoek kenbaar te maken, heeft Fleur deelgenomen aan verschillende congressen o.a. in Kuala Lumpur (KL Vision), Rome en Halifax (IASSID).
Fleur is mijn dochter. Ik weet vanuit mijn eigen (werk)ervaring dat er nog een wereld van onderzoek en ontwikkeling nodig is. Ik hoop dat zij daar een bijdrage aan kan leveren!

Ineke van Wijngaarden-Noordzij

Visual Processing Dysfunctions in Children with Intellectual Disabilities F.H. Boot

Visual processing DYSFUNCTIONS IN CHILDREN WITH INTELLECTUAL DISABILITIES

F.H. BOOT

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Visual Processing Dysfunctions in Children with Intellectual Disabilities

Visual Processing Dysfunctions in Children with Intellectual Disabilities

Visuele verwerkingsproblemen bij kinderen
met een verstandelijke beperking

Proefschrift

ter verkrijging van de graad van doctor aan de
Erasmus Universiteit Rotterdam
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	Prof. dr. C.C.W. Klaver
	Prof. Dr. N.E. Schalij-Delfos

We will take a cup of kindness yet,
For old long past.
- R. Burns -

Contents

1.

General Introduction

General Introduction

One of the outcomes of improved neonatal healthcare worldwide is increased survival of (premature) infants with a high risk of brain pathology caused by, for example, brain malformations, pre- and perinatal asphyxia, or hydrocephalus. Brain pathology can affect several neuronal networks, including the visual system at any level of visual information processing. The medical term that is often used for visual impairment caused by brain pathology is Cerebral Visual Impairment (CVI). CVI is the leading cause of visual impairment in high-income countries (Boonstra et al., 2011; Good et al., 1994; Khetpal & Donahue, 2007) and it is emerging as an important cause in developing countries too (Swaminathan, 2011). The prevalence of CVI is rising and an incidence is reported of 161 in 100,000 children of high-income countries in 2003 (Khetpal & Donahue, 2007). Children with intellectual disabilities are a risk group for visual processing dysfunctions due to brain damage or a brain development disorder. However, no screening program is available for children with intellectual disabilities and the prevalence of CVI in this risk group remains unknown (Evenhuis et al., 2007).

The visual system

Visual information processing

When light enters the eye and falls on the photoreceptors of the retina, it is transformed into action potentials that travel along the axons of ganglion cells within the optic nerves. The primary visual pathways, from retina to the visual cortex, are composed of separate functional streams that pass on information from different types of retinal ganglion cells to the initial stages of cortical processing, see figure 1.1. At the level of the optic chiasm, ~60% of the fibers of both optic nerves cross, reorganize, and are sent to both the left and right side of the brain. The optic nerve fibers on the left side of the brain carry visual information from the right visual field and those at the right side of the brain from the left visual field. The axons first reach the lateral geniculate nucleus, then pass through the optic radiation, and terminate in visual cortex area V1. V1 is the first stage of cortical visual information processing that leads to perception and activation of motor areas to initiate eye movements. Beyond V1, visual information is processed in different functional cortical pathways, see figure 1.2 (Purves et al., 2012). Of the many visual cortical areas, the ventral and dorsal stream have been identified as two major pathways to use as a model for processing visual information. These two streams process different aspects of visual information located in distinct brain areas. The ventral stream, often called the "what" pathway, leads from V1 to the temporal lobes and is involved, amongst others, in visual orientation, memory, and recognition of forms and faces. The dorsal stream, or "where" pathway, leads from V1 to the parietal lobes and is involved in spatial orientation (Ungerleider & Mishkin, 1982). The dorsal

stream is also involved in motion sensitivity, simultaneous perception, and visual motor planning (Dutton, 2003; Goodale & Milner, 1992). Visual information processes that lead to visual perception are collectively called the higher visual functions. The term is used to distinguish these functions from primary visual functions that include, amongst others, visual acuity, contrast sensitivity, and the visual field.

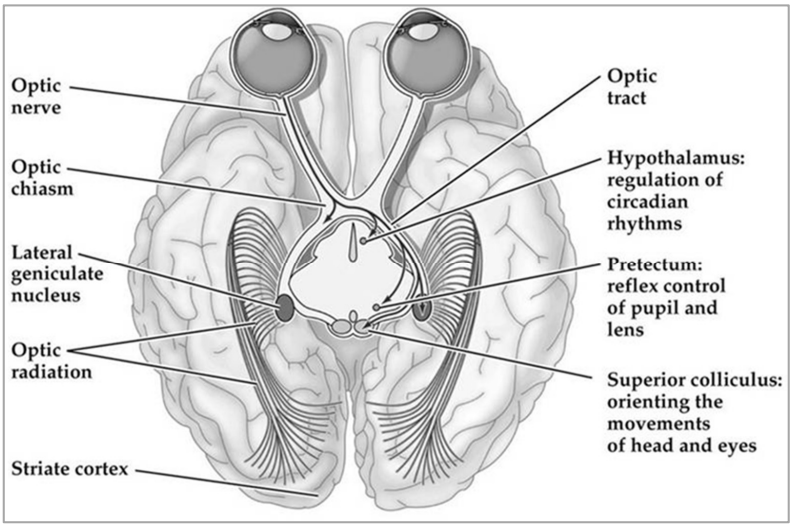

Figure 1.1 - *Visual processing beyond the eye starts with the primary pathways from retina to the visual cortex (view is looking up at the interior surface of the brain) (Purves, 2012).*

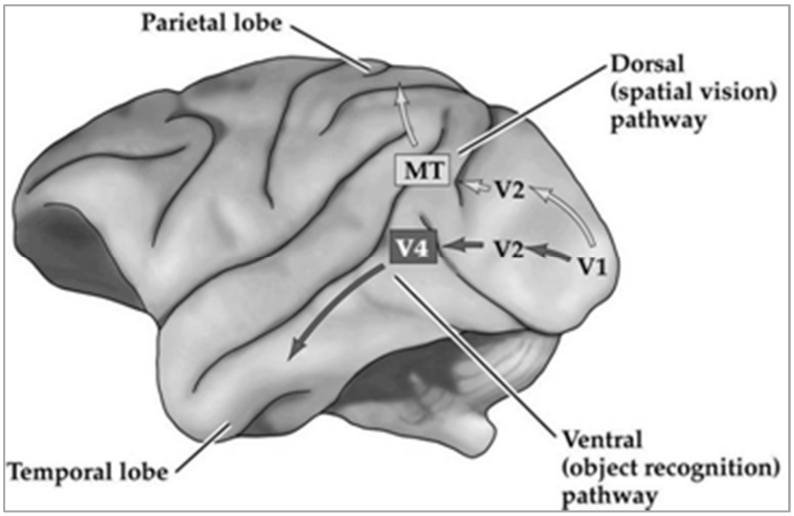

Figure 1.2 *- The ventral and dorsal stream are two described pathways used as a model for processing higher visual functions beyond the visual cortex (V1) (Purves, 2012).*

Eye movement control

To observe the world around us, we constantly make eye movements. Eye movements are important because high visual acuity is restricted to the fovea, the small circular region of the retina. Eye movements allow us to scan the visual field pausing to focus attention on the areas of interest. The rapid orienting eye movements that are made during this scanning are called saccades. These saccades can be elicited voluntarily, or occur reflexively if, for example, danger is entering our visual field. Six extraocular muscles control our eye movements, see figure 1.3. The medial and lateral rectus muscles control horizontal eye movements. Vertical eye movements require the coordinated action of the superior and inferior rectus muscles, as well as the oblique muscles when the eyes are positioned straight ahead. When the eye is abducted (away from the nose), vertical movements are controlled by the rectus inferior and superior. When the eye is adducted (towards the nose), the inferior oblique muscle controls elevation, while depression is controlled by the superior oblique muscle. The vertical muscles are also responsible for torsional movements. The direction of the movement is determined by which eye muscles are activated. The eye muscles are innervated by three cranial nerves, which nuclei are located in the brainstem. These nuclei are connected with, amongst others, the gaze centers in the pons (horizontal gaze center) and midbrain (vertical gaze center). The gaze centers are responsible for generating saccadic eye movements in the correct direction and distance, depending on the projection of the upper motor neurons in the superior colliculus of the midbrain and in the cortical frontal eye field. Processing visual information can activate the motor areas and initiate an eye movement towards the visual stimulus. Ipsilateral and contralateral collaborations between all the different areas involved, enable conjugated saccadic eye movements (Purves, 2012).

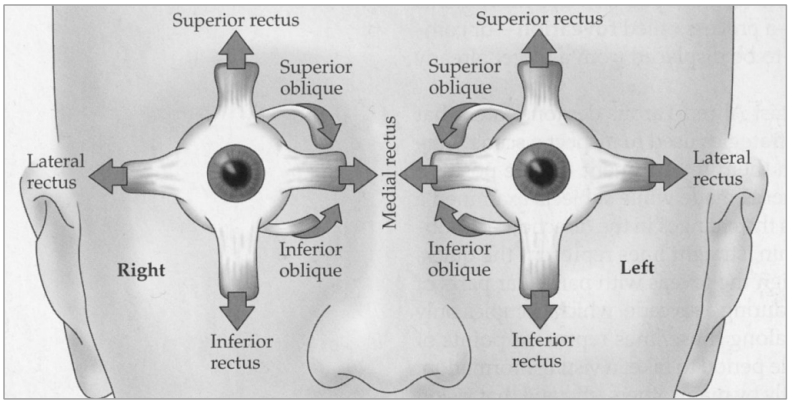

Figure 1.3 *– The six pairs of extraocular muscles to control eye movements (Purves, 2012).*

Assessment of higher visual functions

It has been argued that global form and motion processing can serve as indicators of the ventral and dorsal stream performance (Wattam-Bell et al., 2010). Two common methods to assess form and motion processing in research settings are measurements of Visual Evoked Potentials (VEP) and psychophysical thresholds. VEP is a technique that measures signal transfer and brain activity in the visual pathway, which is often used in infants. Children aged four years and older are generally assessed by psychophysical threshold methods. Here, identification of a presented stimulus is requested to test if the participant has seen and perceived the visual target by giving a verbal or motor response (e.g. pressing a button). Studies using these methods have reported developmental trajectories of form and motion processing during childhood, both with different timelines. Global motion processing seems to take longer before adult levels are reached than global form processing (Gunn et al., 2002). In view of this postnatal maturation of the visual system, it is important to detect dysfunctions at an early age in order to adjust daily support and start individual rehabilitation on time. Visual training and stimulation has been reported to be promising if it is adapted to the individual needs of a child (Vervloed et al., 2006). The aim of early intervention is to improve visual functioning and thereby psychosocial development, daily functioning, and school achievement.

Current diagnostics

Children with brain pathology may have higher visual dysfunctions in combination with ocular motor deficits, such as strabismus or nystagmus, and primary visual dysfunctions, such as low visual acuity or visual field defects. If ocular motor deficits are present, visual input may be altered and this may influence visual functioning. For example, nystagmus may have an effect on the assessment of visual acuity in children, because of the more limited period that the eye is stable enough to allow undisturbed sampling of the visual world (foveation period). Different types of visual dysfunctions can occur in any combination and with any degree of severity depending on type, location, and extent of pathology. However, higher visual functions can also be affected in isolation, in the presence of normal primary visual functions, and without ocular motor deficits. The consequence is that these higher visual dysfunctions can easily be missed (Dutton & Jacobson, 2001; Edmond & Foroozan, 2006; Fazzi et al., 2009).

In The Netherlands, a public vision screening program for children aged 0-19 years has been implemented since 2002. The aim of this screening program is to detect amblyopia, which is caused by strabismus or refractive errors. For children younger than three years the screening is focused on the assessment of basic eye movements, such as pursuit, and on the detection of ophthalmologic disorders. For children aged three years and over, visual acuity is assessed using visual acuity cards (Coenen-van Vroonhoven et al., 2010). However, children with intellectual

disabilities often do not visit the regular maternal and child healthcare centers where this screening is applied (Evenhuis et al., 2007). In addition, the visual acuity cards included in this screening program are often not applicable in children with intellectual disabilities and the screening program only includes the primary visual functions. As stated, higher visual functions can be affected in the presence of normal visual acuity. Nowadays, if a child's higher visual functions are affected, parents sometimes detect "something" is wrong with their child and go and see a physician. Children suspected of higher visual dysfunctions are referred to low-vision rehabilitation centers for further visual function and perception assessment. Diagnostic instruments include neuropsychological tests, which are difficult to perform in very young children (<4 years) and in children with intellectual disabilities. Assessments of visual functions in children with intellectual disabilities are mainly based on observations of visual behavior, for example: which types of materials does the child prefer to watch, can the child distinguish between colors or shapes, or how does he or she react to motion stimuli. Eye movements are judged by the observer to determine if a child has seen the stimulus. The disadvantage of these types of assessments is that they depend on the experience of the professional and do not give a quantitative outcome.

It is still common that ophthalmologists define visual dysfunctions that cannot be explained by ocular disease or damage to the anterior visual pathways as CVI (Fazzi et al., 2009; Khetpal & Donahue, 2007). However, without a neuropsychological assessment that specifies the types of visual processing dysfunctions, the diagnosis CVI does not provide a good starting point for understanding the child's visual problems, starting adequate rehabilitation, and accomplish the best prognosis.

A quantitative approach

Discussions between the departments of Intellectual Disability Medicine and Neuroscience of the Erasmus Medical Center have led to the idea to develop an objective method to assess (reflexive) eye movements using an automatic remote eye tracker (Tobii Technology, Sweden). This idea has resulted in an active collaboration between the two departments, and subsequently Royal Visio became involved as well. The remote eye tracking method allows quantification of visual orienting behavior in terms of reaction time and fixation accuracy. This technique has the advantage to avoid possible subjectivity due to observer bias, which is present in current observation methods. Application in children younger than four years and in children with brain pathology also makes it necessary to use a method that has a low burden for children and does not require difficult instructions, assignments, or verbal responses. Children with abnormal head posture should be able to participate as well. In addition, the method must be applicable in familiar surroundings and the duration of the measurement should be relatively short. Quantification of primary and higher

visual functions in children from a few months old and over makes it possible to create reference values and to investigate development of visual functioning over time.

Main objective

Current facts tell us there is a need to advance the diagnosis of CVI in children with intellectual disabilities based on quantitative parameters. The main objective of this thesis was to obtain the outcome parameters reaction time and fixation accuracy with the automatic remote eye tracker in a typically developing control group, and subsequently use the method to quantify visual information processing in children with intellectual disabilities.

The first aim was to outline if current literature provides information on relations between etiologies of brain damage and higher visual dysfunctions in children. Our second aim was to evaluate the remote eye tracking method in children already diagnosed with visual processing deficits and/or ocular motor disorders based on neuropsychological tests and observations. If the method can be used to distinguish between normal visual processing, impaired visual processing, and impaired ocular motor functions, a second step would be to look further into the different visual processing functions. The third aim was to obtain quantitative data on developmental trajectories of form and motion processing as indicators of the ventral and dorsal stream performance in typically developing children aged 0-12 years (control group). Our fourth aim was to quantify form and motion processing in children with developmental and/or intellectual disabilities aged 0-12 years (risk group) to gain first insights into the presence of higher visual dysfunctions in this risk group. Our fifth aim was to gain more knowledge about possible risk factors of higher visual dysfunctions within a group of children with intellectual disabilities.

2.

Cerebral Visual Impairment: Which perceptive visual dysfunctions can be expected in children with brain damage? A systematic review.

Adapted from:

F.H. Boot, J.M.M. Pel, J. Van der Steen, H.M. Evenhuis

Research in Developmental Disabilities; 2010 (31) 1149–1159

Abstract

Background

The current definition of Cerebral Visual Impairment (CVI) includes all visual dysfunctions caused by damage to, or malfunctioning of, the retrochiasmatic visual pathways in the absence of damage to the anterior visual pathways or any major ocular disease. CVI is diagnosed by exclusion and the existence of many different causes and symptoms make it an overall non-categorized group. To date, no discrimination is made within CVI based on types of perceptive visual dysfunctions. The aim of this review was to outline which perceptive visual dysfunctions are to be expected based on a number of etiologies of brain damage and brain development disorders with their onset in the pre-, peri- or postnatal period.

Methods

For each period, two etiologies were chosen as the main characteristic brain damage. For each etiology a main search was performed. The selection of the articles was based on the following criteria: age, etiology, imaging, central pathology, and perceptive visual function test. The perceptive visual functions included for this review were object recognition, face recognition, visual memory, orientation, visual spatial perception, motion perception, and simultaneous perception.

Results

Our search resulted in 11 key articles. A diversity of research history was performed for the selected etiologies and their relation to perceptive visual dysfunctions. Periventricular Leukomalacia (PVL) was most studied, whereas the main tested perceptive visual function was visual spatial perception.

Conclusion

As a conclusion, the present status of research in the field of CVI does not allow to correlate between etiology, location, and perceptive visual dysfunctions in children with brain damage or a brain development disorder. A limiting factor could be the small number of objective tests performed in children experiencing problems in visual processing. Based on recent insights in central visual information processing, we recommend an alternative approach for the definition of CVI that is based on functional visual processing, rather than anatomical landmarks. This could be of benefit in daily practice to diagnose CVI.

Introduction

When looking at visual dysfunction caused by brain damage or a brain development disorder, the medical term Cerebral Visual Impairment (CVI) is often used (Dutton & Jacobson, 2001). CVI is considered as the number one cause of visual deficit in children of developed countries (Fazzi et al., 2007). Since there has been a significant improvement in the peri- and neonatal care, the survival rate of preterm infants has increased (Stoelhorst et al., 2005). A negative consequence of this progress is an increase of children with brain damage in general and thereby of CVI. Although the term CVI is often mentioned, no sharp definition is available. Commonly, CVI includes all visual dysfunctions caused by damage to, or malfunctioning of, the retrochiasmatic visual pathways in the absence of damage to the anterior visual pathways or any major ocular disease (Fazzi et al., 2009; Khetpal & Donahue, 2007).

However, daily practice reveals that the above definition is not suitable for every patient. People from different disciplines debate about the applicability of CVI, but a distinct consensus is still not reached. This means it remains unclear which patient and for what reason receives a diagnosis of CVI. One of the main reasons that consensus has not been reached is the heterogeneity of causes and symptoms which can be included. In addition, for brain damage or brain development disorders causing CVI different periods of onset exist. This makes CVI an overall extensive non-categorized group, which include many different visual dysfunctions. Other reasons that make it difficult to work with the term CVI are the possible overlap or combinations of peripheral and central nervous system damage, and the high interconnectivity of different brain areas. In humans the visual system starts with the optical component from cornea to retina, followed by the retino-cortical component where neural signals travel from the retina to the primary visual cortex (V1) (Trobe, 2001). Several cortical areas are involved in processing different perceptive visual functions. The occipito-temporal lobes, known as the ventral stream, include object recognition, face recognition, orientation, and visual memory. The occipito-parietal lobes, known as the dorsal stream, include visual spatial perception, motion perception, and simultaneous perception which can be associated with crowding (Dutton, 2003; Trobe, 2001).

Finally, very few objective diagnostic instruments are available, especially for very young children and people with an intellectual disability who are a risk group for cerebral visual dysfunctions. Here for CVI is a likely diagnosis or is diagnosed by exclusion if there is no other explanation. This situation will not benefit the patient for further follow-up and specified visual training. The first objective of this review is to establish if perceptive visual dysfunctions are related to time, character, and location of brain damage. Our second objective is to look at an alternative approach for the definition of CVI based on the different perceptive visual functions. To this end, a systematic review of the available evidence in the scientific literature was conducted to

outline which perceptive visual dysfunctions are to be expected when focusing on a number of etiologies of brain damage and brain development disorders in the pre-, peri- and postnatal period.

Methods

Search methods

Studies were gathered by searches of the computerized databases of PubMed and Embase up to October 2009. Different etiologies of CVI in the pre-, peri- and postnatal period were selected using previous published papers on the etiology, prognosis, and associated neurological and ophthalmic deficits of CVI as a reference (Fazzi et al., 2007; Huo et al., 1999; Khetpal & Donahue, 2007). For each period, two etiologies were included to describe a known cause of CVI in this time period. Khetpal and Donahue (2007) described the occurrence of multiple etiologies in one subject. For the objective of this review the selected etiologies were specifically related to one time period. Former studies, which looked into causes of CVI, showed perinatal hypoxia as the most common etiology (Fazzi et al., 2007; Huo et al., 1999; Khetpal & Donahue, 2007). Therefore, the selected etiologies in the perinatal period are related to perinatal hypoxia. Other etiologies of CVI show different frequencies in literature. For this review, the selected etiologies were listed in the 10 most common etiologies described in literature (Fazzi et al., 2007; Huo et al., 1999; Khetpal & Donahue, 2007). A common cause of CVI is hydrocephalus. Hydrocephalus can originate in all time periods and was therefore not included. Prematurity can be seen as a risk factor for several causes of CVI and is therefore not included as an etiology.

To specify the etiology hypoxia, two known consequences that result in ischemia were described: Periventricular Leukomalacia (PVL) and cerebral hemorrhage. Ischemia is a disruption of blood flow that can cause local brain damage. Ischemia itself can be caused by a reduced cerebral perfusion, which can lead to PVL, or a local decreased blood flow in the brain, which happens in a cerebral hemorrhage. Especially premature newborns are a risk group for this type of injury.

A main search was done for each etiology (see figure 2.1). The diversity of the etiologies reflects the broad spectrum of CVI. We combined three aspects that resulted in the general search string: "Location" AND "Perceptive visual functions" AND "Cause". In Pubmed, "Location" was described with the terms imag*, magnetic resonance imaging, MRI, brain neuroimaging, visuali* and diagnostic imaging (Mesh-term). For "Perceptive Visual Functions" the terms visual, visuo*, dorsal stream, ventral stream, and visual perception (Mesh-term) were included. In Embase, the terms representing "Location" were imag*:ti,ab, visuali*:ti,ab, MRI:ti,ab, magnetic resonance

imaging:ti,ab, CT:ti,ab, computed tomography:ti,ab, brain tomography (Emtree) and nuclear magnetic resonance imaging (Emtree). The terms for "Perceptive Visual Functions" were visual:ti,ab, visuo*:ti,ab, ventral stream:ti,ab, dorsal stream:ti,ab, depth perception (Emtree), movement perception (Emtree), visual orientation (Emtree), spatial orientation (Emtree), recognition (Emtree), and visual memory (Emtree). Tables 2.1A and 2.1B specify the terms representing the "Cause" in respectively Pubmed and Embase. All searches included the limits "All Child: 0–18 years", "Language: English" and "Humans".

The included etiologies were labeled from cause 1 to cause 6 by period of onset, see tables 2.1A and 2.1B. Cause 2, brain development disorder, was subdivided into the different search strings developmental disorders, corpus callosum agenesis, and the syndromal disorders Turner syndrome (45,X0), 22q11.2 deletion syndrome and Williams syndrome. The inclusion of these specifications instead of the more general terms 'congenital disorders of the nervous system' resulted in much more articles on the topic of interest. The syndromal causes were obtained from the Handbook of Neurology, which describes these syndromes in relation to visual spatial difficulties (Aminoff et al., 2008). A wide range of brain development disorders can cause visual dysfunction, but the majority involves ophthalmologic pathology as well which was excluded for this review.

Cause 3, PVL, needs further explanation because here the period of onset is questionable. PVL is a consequence of hypoxia during the pre- or perinatal period and is known to be a common cause of CVI (Jacobson & Dutton, 2000). PVL is more common in premature than term infants and occurs more frequently with decreasing gestational age and size of the newborn. The greatest period of risk for PVL is under 32 weeks of gestational age at birth. PVL may develop prenatally but the main causes of PVL occur perinatally (Deguchi & Miller, 2009). Therefore, in this review, PVL was linked to the perinatal period.

Finally, for each cause the included articles had to describe the same type of brain damage to compare the outcome. As a result, some refinements were made during the search for cause 5, head trauma. Here the articles had to involve closed head injury. Penetrating injury was excluded, as well as head trauma caused by surgery.

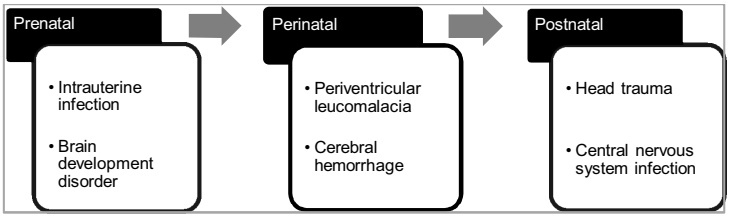

Figure 2.1 - *Selected etiologies of brain damage in children with their onset in the pre-, peri- or postnatal period. The six etiologies are known causes for CVI.*

Table 2.1 (A) - *Search methods and results for each selected etiology by PUBMED (M = Mesh-terms). The etiologies are labeled from cause 1 to 6 by period of onset. The number of included articles is shown after the first and second selection.*

Period	Label	Etiology - search string	No. of hits	Included selection 1	Included selection 2
Prenatal	**Cause 1**	Intrauterine infection Congenital Infection Cytomegalovirus CMV Toxoplasmosis Toxoplasmosis, Congenital (M) Cytomegalovirus Infections/congenital (M) Pregnancy Complications, Infectious (M)	22	0	0
	Cause 2	Brain development disorder			
	2A	Congenital, Hereditary, and Neonatal Diseases and Abnormalities (M) AND Nervous System	114	4	0
	2B	Acrocallosal Syndrome (M) Corpus Callosum	118	9	2
	2C1	Turner Syndrome	13	5	4
	2C2	22q11.2 deletion	11	7	1
	2C3	Williams syndrome	22	2	0
Perinatal	**Cause 3**	Periventricular leukomalacia PVL hypoxia hypoxic-ischemic Leukomalacia, Periventricular (M) Hypoxia, Brain (M) Brain Ischemia (M)	196	45	7
	Cause 4	cerebrovascular incident hemorrhage Hemorrhagic Disease of Newborn (M)	239	14	1
Postnatal	**Cause 5**	Head trauma Brain injury Head injury Craniocerebral Trauma (M)	301	19	2
	Cause 6	Infections of the central nervous system Meningitis Encephalitis Central Nervous System Infections (M)	131	14	0
	Total		**1167**	**119**	**17**

Table 2.1 (B) - *Search methods and results for each selected etiology by EMBASE (E = Emtree). The etiologies are labeled from cause 1 to 6 by period of onset. The number of included articles is shown after the first and second selection.*

Period	Label	Etiology - search string	No. of hits	Included selection 1	Included selection 2
Prenatal	**Cause 1**	Intrauterine infection:ti,ab Congenital Infection:ti,ab Cytomegalovirus:ti,ab CMV:ti,ab Toxoplasmosis:ti,ab Congenital Infection (E) Cytomegalovirus Infection (E) Intrauterine infection (E)	4	0	0
	Cause 2	Brain development disorder			
	2A	Nervous system development (E) Prenatal disorder (E) AND Nervous System	79	6	1
	2B	Corpus Callosum Agenesis (E) Corpus Callosum AND (Absence OR Agenesis):ti,ab	73	2	2
	2C1	Turner Syndrome:ti,ab Turner syndrome (E)	12	0	0
	2C2	22q11.2:ti,ab	7	1	0
	2C3	Williams Syndrome:ti,ab Williams Beuren Syndrome (E)	11	1	0
Perinatal	**Cause 3**	Periventricular leukomalacia:ti,ab PVL:ti,ab hypoxia:ti,ab hypoxic-ischemic:ti,ab Encephalomalacia (E) Brain Hypoxia (E) Brain Ischemia (E)	91	3	0
	Cause 4	cerebrovascular incident:ti,ab Hemorrhage:ti,ab Brain hemorrhage (E) Neonatal Hemorrhage (E)	77	4	1
Postnatal	**Cause 5**	Head Trauma:ti,ab Head Injury:ti,ab Brain Injury:ti,ab Brain injury (E)	167	5	0
	Cause 6	Infections of the central nervous sytem:ti,ab Meningitis:ti,ab Encephalitis:ti,ab Meningitis (E) Encephalitis (E)	78	8	1
	Total		**599**	**30**	**5**

Eligibility

Selection of the articles was based on the following inclusion criteria: original article; participant age between 0 and 18 years old, or a sub group could be derived from the main group; the selected etiology; describing the period of brain damage; describing the location of the brain damage by brain imaging; using a perceptive visual function test; presenting at least one perceptive visual function. Perceptive visual functions included for this review were: object recognition, face recognition, visual memory, orientation, visual spatial perception, motion perception, and simultaneous perception; participants had normal primary visual functions (e.g. acuity, visual fields, color vision) or abnormal primary visual functions, but without pathology of the anterior visual pathway or ocular structures. The common definition of CVI is based on damage to the retrochiasmatic visual pathways and absence of damage to the anterior visual pathways or any major ocular disease. To correlate between CVI and visual outcome, ophthalmologic pathology was a strict exclusion criterion.

The exclusion of articles was based on the following criteria; reviews or comments; ophthalmologic pathology; visual dysfunctions healed by treatment; VEP measurements (Visual Evoked Potentials); ocular motility dysfunction. VEP evaluates the visual pathway up to the primary visual cortex. This involves ocular structures as well as the anterior visual pathway. Ocular motility dysfunction can have many different causes with different locations. This means in some cases that ocular motility dysfunction is caused by ophthalmologic pathology. Thereby, ocular motility problems can influence visual functions, such as visual spatial perception, while the visual processing pathway is normal. References of reviews were screened with the possibility to be included. For Embase, articles already found using Pubmed were excluded.

The first selection of the articles was based on the title and the abstract that had to describe the chosen etiology and main inclusion criteria. The second selection was based on a structured judgment of the criteria in the complete text. Two of the authors independently judged every article. In consultation, consensus was reached for the articles to be included. The number of included articles after the first and second selection is mentioned in tables 2.1A and 2.1B.

Quality assessment

The quality assessment consisted of two types of scoring methods. All articles were assessed for a Level of Evidence (LOE) and for an Extra score. A final score was based on both parts of the quality assessment and the articles were categorized into two groups; (1) articles used as a basis for drawing main conclusions (key articles), and (2) articles with poor quality and poor relation to our objective (complementary articles). These complementary articles were used to confirm or modify the main conclusions.

The LOE score (ranging between 1 and 4) was assessed using the SIGN methodology (Forsyth, 2008). This SIGN methodology is based on the study design and methodological quality. It is used as an epidemiological tool to assess studies including case reports. Using the associated methodology checklist of the SIGN criteria, the sections 'selection of participants', 'confounding' and 'statistical analysis' were involved to score an overall assessment of quality (Forsyth, 2008).
The chosen confounders were age, visual acuity, and IQ. The SIGN criteria were based on the methodology to assess the primary research question, regardless which data was extracted for this review. Meta-analyses, systematic reviews, and RCTs that receive a LOE of 1 were not present. Cross-sectional studies were classified under a LOE of 2. Related LOE scores and the SIGN criteria are listed below:

2++ High quality systematic reviews of case control or cohort studies
High quality case control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal

2+ Well conducted case control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal

2- Case control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal

3 Non-analytical studies, e.g. case reports, case series

4 Expert opinion

Despite the fact that case reports score a low LOE in the SIGN criteria, they can be of high potential value. On the other hand, articles with a high LOE may contain limited information for our objective. Therefore an extra quality criterion was defined and applied to each article for an Extra score (++, + or -). This extra criterion involved three questions that had to be answered with yes or no:
(1) Is the main research question of the article similar to the main question of this review: "Which perceptual visual impairments are expected when looking at moment and character of brain damage in children?";
(2) Are tests used to describe one or more perceptive visual functions designed to test especially these visual functions?;
(3) Does the outcome of the used tests involve quantitative measurements and is the outcome compared with standard reference values or a control group?
The Extra score depended on the total number of questions answered with yes:

++ 3 x Yes

+ 1 or 2 x Yes

- 0 x Yes

The combination of the LOE and the Extra score determined the final score. A key article scored a LOE of 2++ or 2+ in combination with an Extra score of + or ++, e.g. a final score of 2++/+. A LOE of 2- or 3 in combination with an Extra score of ++ resulted into a key article as well. All other combinations were determined as a complementary article. Jacobs et al. (2001) is a case report which scored a LOE of 3. For the extra quality criterion the first two questions were answered with 'No' and the third question was answered with 'Yes'. This lead to a final score of 3/+; a complementary article (see table 2.2).

Data collection

Data of (1) moment of brain damage, (2) medical history of the participants (i.e. etiology), (3) brain imaging results, and (4) visual outcome (perceptive visual functions) were extracted. If only a part of the participants or only sub groups from the total study population were included, data collection was extracted only for these participants or groups.

Results

Study selection

The search of Pubmed resulted in 1167 articles, see tables 2.1A and 2.1B. After the first selection 119 articles remained. After the second selection 17 articles were included, 0–7 articles per cause. Embase resulted in five more articles, 0–2 per cause, see tables 2.1A and 2.1B. A main reason for exclusion was described ophthalmologic pathology. A total number of 22 articles got included for this review, see table 2.2. No articles were included for cause 1, intrauterine infection. Cause 2, brain development disorder, resulted in the highest number of 10 articles that were divided into the specific etiologies of cause 2. Cause 3, PVL, resulted in seven articles and was therefore most studied. The articles with the numbers 11, 14, 15, and 16 (see table 2.2) included the same research group, participants, etiology, and visual functions being tested. The articles used the same type of test method and concluded the same visual outcome. Therefore, these articles were merged together to draw a conclusion. Article number 11 was selected to be described in the results section of this review, because this article is the most recent one. The quality assessment resulted in 11 key and eight complementary articles, see table 2.2.

Table 2.2 - *Total number of included articles and the outcome of the quality assessment. Articles were categorized in key or complementary articles based on the Level of Evidence (LOE) and the extra criterion.*
Key articles: LOE= 2++ / 2+ & extra score= + / ++ or LOE= 3 / 2- & extra score= ++
Complementary articles: LOE= 2++ / 2+ & extra score= - or LOE= 3/ 2- & extra score= + / -

No.	Period	Label	Etiology	Article	Quality		Key or complementary	No. of articles per cause (Key)
					LOE	Extra score		
	Prenatal	**Cause 1**	Intrauterine Infection	x	x	x	x	0 (0)
		Cause 2	Brain development disorder:					
1			*Nervous system development*	Jacobs et al. (2001)	3	+	Complementary	1 (0)
2			*Corpus callosum agenesis*	Herweh et al. (2009)	2-	+	Complementary	4 (0)
3				Corballis et al. (2000)	3	+	Complementary	
4				Panos et al. (2001)	3	-	Complementary	
5				Fiorentini et al. (1992)	3	+	Complementary	
6			*Turner syndrome*	Kesler et al. (2004)	2+	++	Key	4 (3)
7				Haberecht et al. (2001)	2+	++	Key	
8				Reiss et al. (1995)	2++	+	Key	
9				Reiss et al. (1993)	3	+	Complementary	
10			*22q11.2 deletion syndrome*	Stiers et al. (2005)	3	++	Key	1 (1)
11	**Perinatal**	**Cause 3**	Periventricular leukomalacia	Pavlova et al. (2009)	2++	++	Key	6 (3)*
12				Morrone et al. (2008)	3	++	Key	
13				Pavlova et al. (2007)	2++	++	Key	
14				Pavlova, Marconato et al. (2006)	2++	+	Key	
15				Pavlova, Sokolov et al. (2006)	2++	+	Key	
16				Pavlova et al. (2005)	2++	+	Key	
17		**Cause 4**	Cerebral hemorrhage	van den Hout et al. (2004)	2+	+	Key	2 (2)
18				Ross et al. (1996)	2++	+	Key	
19		**Cause 3 & 4**		Pike et al. (1994)	2+	+	Key	1 (1)**
20	**Postnatal**	**Cause 5**	Head trauma	Braga et al. (2007)	3	+	Complementary	2 (0)
21				Roberts et al. (1995)	3	-	Complementary	
22		**Cause 6**	Central nervous system infection	Valtonen et al. (2008)	3	++	Key	1 (1)

** Articles for cause 3 with the numbers 11, 14, 15 and 16 count for 1 article; ** Article number 19 is used for cause 3 and 4.*

Outcomes

To keep an overview of CVI based on time period and cause of the brain damage or brain development disorder, the results are presented per etiology. The key articles are described here and tables 2.3A – 2.3C show the outcomes in detail.

Cause 1 – intrauterine infection

None of the articles met the inclusion criteria.

Cause 2 – brain development disorder

For this cause 10 articles met the inclusion criteria. Four were categorized as key articles (Haberecht et al., 2001; Kesleret al., 2004; Reiss et al., 1995; Stiers et al., 2005) and six as complementary articles (Corballis & Finlay, 2000; Fiorentini et al., 1992; Herweh et al., 2009; Jacobs et al., 2001; Panos et al., 2001; Reiss et al., 1993). The key articles on Turner syndrome showed deficits of visual spatial perception and visual memory. The type of tests used for measurements of visual spatial perception were the JLO test (Judgment of Line Orientation) and the WCJ-SR test (Woodcock–Johnson Spatial Relations). The ROCF test (Rey-Osterrieth Complex Figure) was used to determine both visual spatial perception and visual memory. The one complementary article describing Turner syndrome was Reiss et al. (1993), which study concluded reduced face recognition and visual spatial perception but normal visual memory in a child with Turner syndrome. Overall, reduced visual spatial perception was found in children with Turner syndrome. Stiers et al. (2005) assessed a child with 22q11.2 deletion syndrome and his score on several perceptive visual functions, including object recognition, face recognition, visual spatial perception, and visual memory. This study used a part of the visual perceptual battery L94 (Stiers et al., 2001), the JLO test, the FACE test (face recognition), and the CMS test (Children's Memory Scale). The case showed specific impairment at two tests for object recognition and some problems with face recognition. Visual spatial perception and visual memory were tested as normal. The complementary articles included for cause 2 did not describe children with 22q11.2 deletion syndrome. Therefore, these articles could not be used to confirm or modify the main conclusion.

Cause 3 – Periventricular Leukomalacia (PVL)

For this cause four articles met the inclusion criteria and all were categorized as key articles (Morrone et al., 2008; Pavlova et al., 2009; Pavlova et al., 2007; Pike et al., 1994). Participants were diagnosed with PVL based on MRI findings. PVL is characterized by bilateral gliosis of the white matter and tissue loss affecting the regions around the lateral ventricles, with secondary ventricular dilatation (Deguchi & Miller, 2009; Volpe, 2001). This refers directly to the location of the brain damage. The articles on PVL showed deficits of motion perception, orientation, crowding ratio, and visual spatial perception. The type of test used for measurements of orientation was the LA test (Labyrinth test). Crowding was measured using the crowding ratio and visual spatial

perception was measured using the Stereo Depth test (SD). Pike et al. (1994) described children with PVL, cerebral hemorrhage, or cerebral infarction. Three children with PVL met the inclusion criteria for this review. Motion perception was the single visual function tested in more than one article. Pavlova et al. (2009) and Morrone et al. (2008) both showed reduced motion perception using the Detection task (DT) with camouflaged body motion, the Random dot kinematogram (RDK), Sinusoidal gratings (SG), and the Driving simulation (DS). Morrone et al. (2008) studied two cases of children with PVL, but only one case, patient G.B, fulfilled the inclusion criteria. Overall, reduced motion perception was found in children with PVL.

Cause 4 – cerebral hemorrhage

For this cause, three articles met the inclusion criteria and all were categorized as key articles (van den Hout et al., 2004; Pike et al., 1994; Ross et al., 1996). The articles on cerebral hemorrhages showed deficits of object recognition, visual spatial perception, visual memory, and crowding ratio. All three articles investigated different perceptive visual functions. Therefore, correlations could not be found. Van den Hout et al. (2004) assessed children with unilateral periventricular hemorrhage or PVL. Only the cases with cerebral hemorrhage met the inclusion criteria (group 1, n=7). This study measured object recognition and visual spatial perception using the visual perceptual battery L94 (Stiers et al., 2001). Ross et al. (1996) investigated children with subependymal or intraventricular cerebral hemorrhage (S/IVH) and their visual memory, using the Invisible Displacement task (ID). This task features two items; the invisible displacement (ID) trial and the systematic search (SS) trial. Pike et al. (1994) described children with PVL, cerebral hemorrhage or cerebral infarction. Six children with IVH met the inclusion criteria for this review. Crowding was measured using the crowding ratio.

Cause 5 – head trauma

For this cause two articles met the inclusion criteria, which were both categorized as complementary articles (Braga et al., 2007; Roberts et al., 1995). Therefore, no main conclusion could be drawn for postnatal head trauma in children. Both complementary articles did show reduced visual memory.

Cause 6 – central nervous system (CNS) infection

For this cause one article met the inclusion criteria, which was categorized as a key article (Valtonen et al., 2008). Valtonen et al. (2008) assessed one child with a postnatally acquired herpes encephalitis infection at the age of 3 years. The subject's object recognition and visual spatial perception were reduced. Various tasks were performed such as the BORB (Birmingham Object Recognition Battery), the DTVP-2 (Developmental Test of Visual Perception), the VMI (Visual Motor Integration), and several line orientation tasks. Since there was only one article included for a postnatal CNS infection, correlations could not be found.

Table 2.3 (A) - *Overview of the visual outcome related to the location and etiology of the brain damage or brain development disorder in the prenatal period (Key articles). OR: object recognition; FR: face recognition; VM: visual memory; OR: orientation; VSP: visual spatial perception; MP: motion perception; SP: simultaneous perception; CR: crowding.*

Label		Article	Type of imaging	Location brain damage	visual functions (type of test)	Test results	Visual outcome
Cause 1	Intrauterine infection	x	x	x	x	x	x
Cause 2	Brain development disorder:						
	Turner syndrome	Kesler (2004)	fMRI	Dysfunction of the neural systems in the parietal-occipital areas and the prefrontal cortex	VSP (JLO - neuro)	Cases (n=13): 23±9* Controls (n=12): 28±3	Reduced visual spatial perception
					VSP (JLO - easy)	Cases (n=12): 14±4 Controls (n=12): 18±5	
					VSP (JLO - diff)	Cases (n=12): 16±10* Controls (n=12): 25±4	
		Haberecht (2001)	fMRI	Bilateral prefrontal cortex, the caudate head, the supra marginal gyrus of the parietal lobe	VSP (JLO)	Cases (n=11): 18±9* Controls(n=14): 25±4	Reduced visual spatial perception
					VSP (WCJ-SR)	Cases (n=11): 50±12* Controls (n=14): 63±7	
		Reiss (1995)	MRI	Bilateral parietal region	VSP (JLO)	Cases (n=28): -1.68±1.65* Controls (n=28): 0.27±1.1	Reduced visual spatial perception & visual memory
					VSP & VM (ROCF)	Cases (n=26): -2.13±2.0* Controls (n=26): -0.63±1.0	
	22q11.2 deletion syndrome	Stiers (2005)	(f)MRI	Between the anterior lateral ventricle and the deep folds of the inferior frontal gyrus, right inferior parietal lobe, right superior occipital lobe	OR (L94 - OVERL)	Cases (n=1): -1.28**	Reduced object & face recognition
					OR (L94 - NOISE)	Cases (n=1): -0.52	
					OR (L94 - VIEW)	Cases (n=1): -1.95**	
					OR (L94 - DEVOS)	Cases (n=1): -1.04	Normal visual memory & visual spatial perception
					OR & VM (L94 - VISM)	Cases (n=1): +0.45	
					VSP (L94 - BLOCKM)	Cases (n=1): -0.12	
					VSP (JLO - pre)	Cases (n=1): -0.11	
					FR (FACE)	Cases (n=1): -1.02	
					VM (CMS - DL)	Cases (n=1): +0.67	
					VM (CMS - DIR)	Cases (n=1): -0.67	
					VM(CMS - DDR)	Cases (n=1): +0.33	
					VM & FR(CMS - FIR)	Cases (n=1): -1.00	
					VM & FR (CMS - FDR)	Cases (n=1): -1.33**	

** Significant; ** Below 10th percentile.*

Table 2.3 (B) - *Overview of the visual outcome related to the location and etiology of the brain damage in the perinatal period (Key articles). OR: object recognition; FR: face recognition; VM: visual memory; OR: orientation; VSP: visual spatial perception; MP: motion perception; SP: simultaneous perception; CR: crowding.*

Label	Etiology	Article	Type of imaging	Location brain damage	visual functions (type of test)	Test results	Visual outcome
Cause 3	Periventricular leukomalacia	Pavlova (2009)	MRI & MEG	Bilateral parieto-occipital periventricular & right temporal and frontal cortex	Biological MP (DT)	Cases (n=8): 2.29±0.67* Controls (n=10): 3.13±1.22	Reduced motion perception
		Morrone (2008)	(f)MRI	Bilateral periventricular and posterior corpus callosum, bilateral inferior temporal sulcus	MP (RDK - circular)	Cases (n=1): normal score	Reduced motion perception & inversion of translational motion perception
					MP (RDK - radial)	Cases (n=1): normal score	
					MP (RDK - translational)	Cases (n=1): inversion of direction, perfectly incorrect discrimination	
					MP(SG)	Cases (n=1): showed no inversion. But the contrast sensitivity reduced rapidly with a higher spatial frequency	
					MP (DS)	Cases (n=1): saw the moving objects too late	
		Pavlova (2007)	MRI	Bilateral periventricular with right parieto-occipital & frontal extent	OR (LA)	Cases (n=11): 4.818±4.167* Controls (premature, n=8): 9.375±3.503 Controls (term, n=8): 10.125±3.314	Reduced orientation
		Pike (1994)	Ultrasound & MRI	Bilateral periventricular	CR (ratio)	Cases (n=3): 2.0, 1.5, 2.0 (=67%)** Controls (n=5): 1.5, 2.0, 1.0, 1.5, 1.5 (=20%)	Crowding and reduced visual spatial perception
					VSP (SD)	Absence of stereoscopic vision was more common in cases than in cerebral hemorrhages or controls	
Cause 4	Cerebral hemorrhage	van den Hout (2004)	MRI	Periventricular parenchym, right or left sided (right: n= 4, left: n=3)	OR & VSP (L94 battery)	Cases (n=7) with right sided hemorrhages (n=4) showed deficits. One failed on DEVOS and VIEW. The other three failed on OVERL & BLOCKC	Reduced object recognition and visual spatial perception
		Ross (1996)	Ultrasound	Subependymal and intraventricular. Grade 1 = isolated germinal matrix hemorrhage or Grade 2 = 1 plus extension into the ventricles but no dilatation.	VM (ID - ID trial)	Cases (n=27): 3.9±1.7*** Controls (premature, n=28): 5.2±1.3 Controls (term, n=27): 5.3±1.6	Reduced visual memory
					VM (ID - SS trial)	Cases (n=27): 1.5±1.2**** Controls (premature, n=28): 1.6±1.2 Controls (term, n=27): 2.4±1.2	
		Pike (1994)	Ultrasound & MRI	Intraventricular	CR (ratio)	Cases (n=6): 1.5, 2.0, 1.5, 2.0, 1.33, 1.33 (=33.33%)** Controls (n=5): 1.5, 2.0, 1.0, 1.5, 1.5 (=20%)	Crowding

** Significant; ** Abnormal; *** Significant to both control groups; **** Significant to the term control group.*

Table 2.3 (C) - *Overview of the visual outcome related to the location and etiology of the brain damage in the postnatal period (Key articles). OR: object recognition; FR: face recognition; VM: visual memory; OR: orientation; VSP: visual spatial perception; MP: motion perception; SP: simultaneous perception; CR: crowding.*

Label	Etiology	Article	Type of imaging	Location brain damage	Measured visual functions (type of test)	Test results	Visual outcome
Cause 5	Head trauma	x	x	x	x	x	x
Cause 6	Central nervous system infection	Valtonen (2008)	MRI	Bilateral occipital and parietal cortex	OR (BORB - fore) OR (BORB - mini) VSP (BORB - line A) VSP (BORB - line B) VSP (BORB - circle A) VSP (BORB - circle B) VSP (VMI) VSP (line orientation)	Cases (n=1): 15/25* Cases (n=1): 20/25** Cases (n=1): 19/30* Cases (n=1): 23/30* Cases (n=1): 24/30** Cases (n=1): 25/30 Cases (n=1): at age 15 an age equivalent of 5 years Cases (n=1): profound impairment with any degree of complexity and left-right mirror reflections	Reduced object recognition & visual spatial perception

** Score 2 SD or more below published control data; ** Score 1 SD or more below published control data.*

Discussion

This review presents an overview of CVI and describes six different etiologies known for CVI and their relation to the period of onset, location, and perceptive visual dysfunctions. Because CVI is currently an overall non-categorized diagnosis and no consensus has been made about its application, this overview is of use in clinical practice. We found diversity in the history of research performed for the selected etiologies and their relation to perceptive visual dysfunctions. Amongst the included articles a variation was found in the type of visual functions that were tested. This makes it difficult to compare papers that deal with a particular etiology. In all articles, with the exception of one, tests were limited to only one or two visual functions. In most papers visual spatial perception was measured and described. However, if only one perceptive visual function is tested, it remains unclear how this person would score on other visual functions. Nevertheless, in our review we present positive results and answers that correspond to our main objectives.

For Turner syndrome the location of the brain development disorder is mainly in the parietal area and prefrontal cortex. This has been demonstrated in other studies (Walter et al., 2009). Walter et al. (2009) describes decreases in volume in the occipital and parietal cortices, specifically in superior parietal and post central gyri, and reduced activity of the fronto-parietal network using functional imaging. All studies on Turner syndrome described a reduced performance on visual spatial perception, which is consistent with former research (Walter et al., 2009).

The one case describing 22q11.2 deletion syndrome showed a brain development disorder of the anterior lateral ventricle, the inferior frontal gyrus, the right parietal, and occipital lobe. According to Stiers et al. (2005), the morphological abnormalities found in this case do not agree with those found in other studies. Brain areas that appear to be most affected in 22q11.2 deletion include a decreased size of the cerebellar vermis, larger amygdale, and increased incidence of cavum septum pellucidum (Walter et al., 2009). This difference may be due to the fact that this was a single subject analysis. Differences in imaging results between studies with 22q11.2 deletion syndrome are also described in Walter et al. (2009). This suggests that for each individual with 22q11.2 deletion syndrome there is variable brain development disorder. Visual spatial deficits are known in participants with 22q11.2 deletion syndrome, but in this case described by Stiers et al. (2005) the visual spatial perception was tested as normal. Another contrast to other studies is the normal visual memory described in Stiers et al. (2005). Simon et al. (2005) concluded significant poorer performance on visual memory compared to verbal memory. This also may be due to the single subject analysis. Recently published literature on visual recognition in relation to 22q11.2 deletion is not available.

The location of PVL is always based in the periventricular region, especially in the parieto-occipital area. All four articles describe the damage in the periventricular region, but the extent of the lesion differs. The different visual dysfunctions found in the included articles may be explained by the fact that PVL can involve both the ventral and the dorsal visual streams (Fazzi et al., 2009). The article that describes reduced visual navigation performance, which is regarded as a ventral stream dysfunction, does not show a particular location of the brain damage in the parieto-temporal area. This can be explained by the fact that the periventricular area contains many interconnecting fibers and that it is the brain connectivity that is damaged rather than a single brain structure.

The locations of the hemorrhages described in the articles are in the periventricular region, like PVL, or in the intraventricular region. Both ventral stream and dorsal stream dysfunctions are described in the articles, which is possible following the lesion site.

The case report of Valtonen et al. (2008) does not describe the type of herpes infection which the subject is treated for. In view of the fact that it has been shown that different type of herpes viruses affect different regions of the brain (Noguchi et al., 2010), a comparison with literature for the location is difficult. In this article, damage of the bilateral occipital and parietal cortex is related to deficits in object recognition and visual spatial perception. This is not expected when both ventral and dorsal stream are involved. Reduced object recognition is described elsewhere in a case with encephalitis of unknown origin, where lesions in the occipito-parietal and occipito-temporal regions are shown (Le et al., 2002).

With the available literature this review does not cover a complete overview of CVI. Not every known cause for CVI has been described here and for some causes research regarding perceptive visual functions has not been performed completely or is not available. For the causes intrauterine infection and head trauma none or only complementary articles were found. This means more specific research on these topics should be performed to complement the overview. Furthermore, the lack of the application of a unified test battery that includes testing most of the visual functions makes the overview incomplete.

In the design of this review we decided to include as many articles as possible. A broad range of imaging, visual tests, and subject characteristics were included. Four studies used fMRI as an imaging tool (Haberecht et al., 2001; Kesler et al., 2004; Morrone et al., 2008; Stiers et al., 2005). This method makes it possible to relate a location to the visual function being measured at that time. Using structural MRI limits the conclusion of the location because it is not certain that the lesion seen on MRI really caused the visual dysfunction which was reported. Especially when looking at children with multiple disabilities. Furthermore, not all lesions which cause CVI can be seen on MRI. Another aspect to be considered is the large age range. The age of the participants ranged from 0 to 18 years and different aspects of visual development take place during this period of life. Although age was included as a confounder in the quality assessment, age was not a

limiting factor when different articles were compared. The confounders for this review were subjectively chosen and other confounding factors could have been included, such as gender, income or class, and follow-up. But the overall outcome of the quality assessment would not differ when more or all types of confounders were included. Discussing the criteria, ophthalmological damage was often seen as an exclusion criterion for an article. However, to work with the common definition of CVI this exclusion criterion was inevitable. This should be taken into consideration when doubting the efficacy of the known definition based on anatomical landmarks.

Conclusion

Why is CVI in the general definition limited to anatomical landmarks? What if the definition for CVI is not based on location, but on the visual dysfunctions? From the results of this review we state that CVI based on anatomical landmarks is illogical in theory and in practice.

Firstly, the strong interconnectivity in the brain between the visual pathways makes it almost impossible to dissociate these areas. To assign a particular visual dysfunction to a single brain structure is not possible since (1) multiple areas are involved, (2) possible overlap of lesions complicates a clear anatomical delineation, and (3) a combination of peripheral and central damage is often seen in one patient.

Secondly, it has recently been shown that peripheral defects can also influence central visual information processing. Simonsz et al. (2009) have shown that congenital nystagmus occurs in cases where the rod ON-bipolar cells are not receiving a proper synaptic input and inner retinal processing seems to be compromised. Congenital nystagmus is generally known as a central disorder caused by instability in the velocity-to-position integrator and is directly related to faults in motion processing. This means if a peripheral lesion can cause nystagmus, perhaps other central functions, such as the perceptive visual functions, can be affected by defects at the level of the retina as well.

In conclusion, labeling a child with a very broad diagnosis of exclusion such as CVI should be revised. We recommend an alternative definition of CVI that is based on functional visual processing. We feel that a separate description of the types of visual dysfunctions could be useful and a good addition in clinical practice. This means that the visual dysfunctions should be quantified in children with specific medical history in combination with signs of impairment of perceptive visual tasks in daily life. Future studies will be needed to explore the application of objective methods to assess abnormal perceptive visual functions in young children and people with an intellectual disability.

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3.

Effects of visual processing and congenital nystagmus on visually guided ocular motor behavior

Adapted from:
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Abstract

Background

The aim of this study was to compare visually guided ocular motor behavior in children with visual processing and/or motor deficits with an age-matched comparison group and an adult group.

Methods

Visual stimuli were shown to 28 children with visual processing and/or motor deficits (11 females, 17 males; mean age 7y 5mo, SD 2y 9mo, range 2–14y) and an age-matched comparison group of 213 typically developing children (115 females, 98 males; mean age 5y 8mo, SD 3y 5mo, range 0–12y). The adult group consisted of nine females and two males with (mean age of 24y 4mo, SD 4y 8mo). Individuals who had a likely diagnosis of cerebral visual impairment (CVI), an opticopathy with unknown location, nystagmus, glaucoma, or a cataract were included in the study. Exclusion criteria were a visual acuity below 0.2, a developmental age under one year, and the presence of brain tumors, autism, and anxiety disorders. Orientating eye movements to large cartoons were quantified using the reaction time to fixation (RTF) and gaze fixation area (GFA). A Mann–Whitney U test was used to compare the differences between groups and Bonferroni post-hoc testing was used to analyze age dependence of RTF and GFA values within the comparison group.

Results

Individuals with CVI showed significantly prolonged RTF values; those with congenital nystagmus showed significantly increased GFA values. In the comparison group, RTF was significantly longer in children under the age of two years than in children aged four years and older (290 and 200 ms respectively; $p<0.001$). No developmental change was found for GFA values.

Conclusion

Increased RTF values in individuals with CVI relate to visual processing deficits. The data suggest that visually guided ocular motor responses mature during the first three years of life.

Introduction

Early human development involves the maturation of complex interactions between cortical networks that are specialized for target selection (visual system), motor preparation (pre motor system), and generation of eye movements (ocular motor system) (Corbetta et al., 2008; Sommer & Wurz, 2008). Recently, two areas have been described that act as attention networks: a dorsal frontoparietal network and a ventral frontoparietal network (Corbetta & Shulman, 2002). It is proposed that the dorsal network enables the selection of goal-driven (voluntary) attention, whereas the ventral network detects stimulus-driven (reflexive) attention (Corbetta & Shulman, 2002). Activation in the dorsal premotor region, the frontal eye field, and the superior parietal cortex was shown during voluntary or reflexive shifts of attention. This suggests not only involvement of multiple brain areas but also dynamic interaction between the cortical attention networks (Corbetta et al., 2008; Rosen et al., 1994). After selection of a target of interest, command signals from the cortex reach the brainstem and activate the superior colliculus, which initiates goal-directed eye (and head) movements (Wurtz & Goldberg, 1971).

During the first months of human life, the visual (Atkinson, 1992; Mercuri et al., 2007) and the ocular motor system (Canfield et al., 1997; Gredebäck et al., 2006; Gredebäck et al., 2004; Rosander & von Hofsten, 2002) undergo substantial developmental changes. The speed and accuracy of visual processing have been assessed in infants, children, and adults with electrophysiological techniques, such as visual evoked potentials (VEP). A typical measure in pattern-reversal VEP is the p100 latency, which represents the integrity of the primary visual pathway from the retina to the cortex. It was found that this latency fell from around 250 ms in 3-month-old infants to approximately 100 ms in children aged two years and older (McCulloch et al., 1999). This suggests maturation of the visual system in the first two years of life. Less well known is at what age the human ocular motor system matures with respect to controlling saccades for detecting and fixating visual targets (Mercuri et al., 2007; Fischer et al., 1997). Ocular motor responses have been characterized in terms of saccade reaction times (SRTs) and fixation accuracies of visually guided (reflexive) saccades in infants and children (Canfield et al., 1997; Fukushima et al., 2000; Gredebäck et al., 2006; Roucoux et al., 1983; Yang et al., 2002). In a longitudinal study it was shown that SRT values decreased from 595 ms at four months of age to 442 ms at eight months of age during the tracking of abruptly changing trajectories (Gredebäck et al., 2006). Others have tested visually guided (reflexive) saccades in children aged four years and older by presenting small light-emitting diode lights in a dimmed environment. These studies found a rapid decline of SRT values during the first year of life (e.g. from approximately 600 ms at age 4mo to around 400 ms at age 8mo) and a more gradual decline in SRT values in children aged between four years and older (Fukushima et al., 2000). The large differences between p100

latency values and SRT values suggest that the critical factor for maturation of visually evoked orientating behavior is in the ocular motor preparation stage. Finally, it has been shown in human infants that visual target fixation is accomplished by a head rotation accompanied by a series of small eye saccades (Roucoux et al., 1983).

The aim of the present study was to compare orientating behavior in individuals with visual processing and/or motor deficits with an age-matched, typically developing comparison group. When damage occurs in (parts of) visual processing areas, specific visual information processing can be disturbed, depending on the location of the lesion. This may result in a delay in the processing of visual information. A collective name for deficits in higher visual processing is cerebral visual impairment (CVI), which is commonly defined as a loss of visual function without damage to the anterior afferent visual pathways or ocular structures. Disturbances in motor command signals lead to problems and delays in eye motor control. An ocular motor disorder that presents within six months of birth is known as congenital nystagmus. Nystagmus involves involuntary oscillatory horizontal, vertical, or rotational eye movements. The motor response systems (fixation and pursuit) seem to function correctly during foveation periods, but individuals with congenital nystagmus have altered visual input, which leads to a decrease in visual acuity and an increase in thresholds for visual target and motion detection (Abadi et al., 1999; Hertle et al., 2002). This study hypothesizes that fixation of new visual targets is delayed in individuals with CVI or congenital nystagmus relative to comparison groups, and that individuals with congenital nystagmus have increased fixation areas as a result of eye movement instabilities.

Methods

Participants

For this study, 29 children were recruited from the Royal VISIO in Rotterdam (a Dutch organization for people who are blind or visually disabled) and 10 children were recruited from the Rotterdam Ophthalmic Institute (Rotterdam Eye Hospital, Rotterdam, the Netherlands), with the aim of including individuals with an increased risk of visual processing deficits and/or eye motor deficits. The participants were aged between two and 14 years and had to meet one of the following criteria for inclusion: a likely diagnosis of CVI, an opticopathy with unknown location, nystagmus, glaucoma, or cataract. Exclusion criteria were visual acuity below 0.2, a developmental age under one year, and the presence of brain tumors, autism, or anxiety disorders. Parents were informed about the study objective and measurement procedure, and were asked to give written consent for participation and review of medical records; written consent was received from 35 participants. Four individuals were unable to attend and three individuals refused to participate on

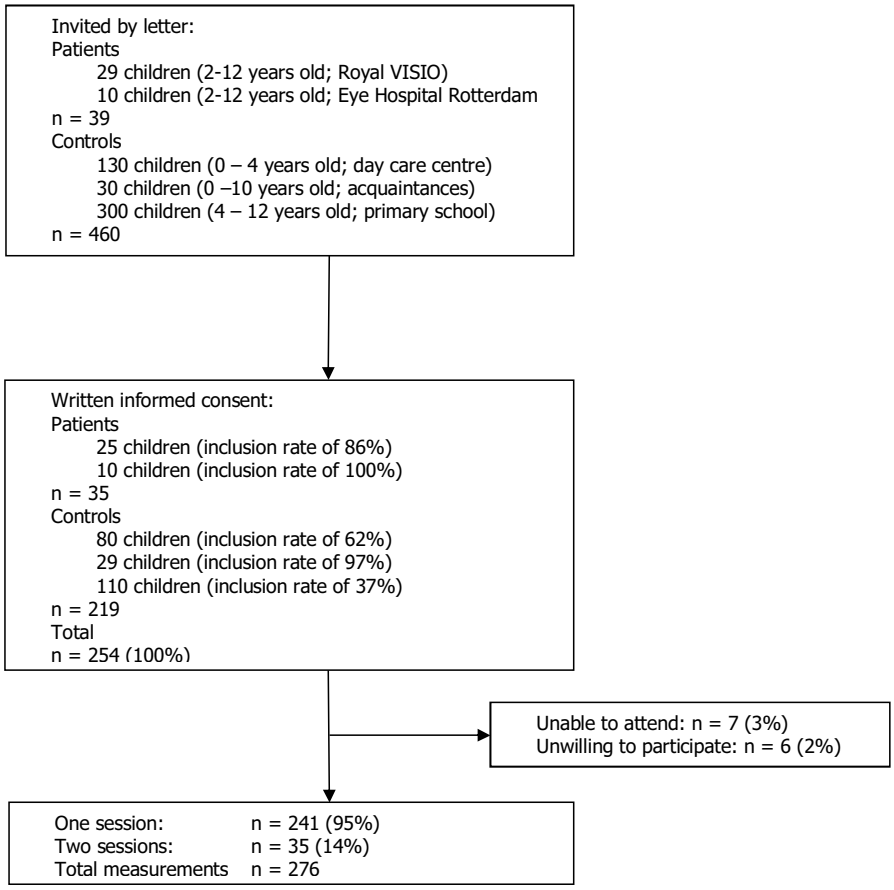
the day of the measurement, resulting in a final total of 28 participants (see figure 3.1). Information regarding gestational age, medical history, ophthalmological disorders, and development, was obtained from medical records and questionnaires. The participants were divided into two groups: a group with congenital nystagmus comprising 11 individuals and a group with CVI comprising 12 individuals. Participants with CVI had a high risk of having brain damage (an event in their medical history or an intellectual and/or motor disability). The comparison group of 460 typically developing individuals aged between 0 and 12 years was recruited in the Rijnmond region, Rotterdam. Parents were informed about the study and written consent was received for 219 (48%) participants. Individuals with a history of developmental or neurological disorders or learning disability were excluded from the comparison group. At the time of measurement, three children from the comparison group were unable to attend and three refused to participate, resulting in a comparison group of 213 individuals (see figure 3.1). The results presented here are part of a large study that has not yet been completed.

All participants had normal or corrected-to-normal vision, as care was taken that the vision of all participants was corrected using glasses. Short cartoons of relatively large and high-contrast were shown on a remote eye-tracking monitor. The cartoons were part of a block of short films used to investigate orientating behavior, visual attention, and form and motion coherence. One session was successfully shown to 28 participants (11 females, 17 males; mean age 7y 5mo, SD 2y 9mo) and to the comparison group (115 females; 98 males; mean 5y 8mo, SD 3y 5mo). A second session was successfully shown to a subgroup of 35 comparison children for a test–retest analysis. The data from the first successfully measured session in each participant are presented here. The performance of the comparison group and the performance of 11 typically developing adults (nine females; two males; mean age 24y 4mo, SD 4y 8mo) were compared. The adult group was included to test if visually guided ocular motor behavior evolved after the age of 12 years. Experimental procedures were approved by the medical ethics committee of the Erasmus University Medical Center, Rotterdam, The Netherlands (METC-2006-055) and adhered to the Declaration of Helsinki for research involving human participants.

Measurement set-up and procedures

The set-up consisted of a 17-inch monitor with an integrated infrared eye-tracking system (Tobii 1750; Tobii Corporation, Danderyd, Sweden). The monitor was positioned against a plain background. In children aged up to four years, side panels reduced any visual distraction from the monitor. The youngest children (aged between 4mo and 12mo) sat on a parent's or investigator's lap. Otherwise, each child sat in a comfortable chair at a distance of 60 cm from the monitor to ensure efficient tracking of the eyes. The experiments were conducted in a quiet room in ambient light conditions. The eye tracker measured the gaze position of each eye separately using cornea

Figure 3.1 - *A flow chart of the study illustrating the inclusion of the patients and healthy controls and the number of the successfully measured first and second trials.*



reflection at 50Hz. The system's latency was ±30 ms, which compensated for free head movements, allowing a visual angle towards the monitor of 30° x 24° (1280 x 1024 pixels). First, a standardized five-point calibration procedure was performed for both eyes. An accompanying brief sound (a ringing doorbell) directed attention towards the monitor during calibration of the youngest children. Next, a session of about 12 minutes was shown with the goal of randomly presenting visual targets for testing basic eye movements, such as pursuit, and (higher order) visual perception, such as form and motion coherence and competitive and non-competitive dots. All measurements were stored on a hard disk and eye movement data were analyzed offline using self-written Matlab programs (Mathworks, Natick, MA, USA).

Data analysis and statistics

The cartoons were selected, with permission, from a cartoon collection by Dick Bruna (creator of Miffy the rabbit). Each cartoon had a visual angle of 4.5° x 9.0° (width x height) and moved 1.5° up and 1.5° down at a constant speed of 3° per second. In total, 24 cartoons were shown, six cartoons per monitor corner, each for at least two seconds with a maximum duration of 10 seconds. The reaction time to fixation (RTF) of each cartoon was defined as the time that gaze was within 6° from the cartoon center (Pel et al., 2010). Fixation performance was defined as 85% of all gaze coordinates within the target areas using principal component analysis (Oliveira et al., 1996). The gaze fixation area (GFA) was expressed as a mean diameter in degrees. The differences between the participants and the comparison group were tested for significance using the Mann–Whitney U test. Data per age-based subgroup were checked for normal distribution using the Kolmogorov–Smirnov test. An analysis of variance was performed to test whether differences between age groups existed for minimum RTF (RTF_{min}), maximum RTF (RTF_{max}), and GFA values. A Bonferroni multiple comparison (post-hoc) test using a threshold for significance of 0.05 was performed to identify those age groups that significantly differed from the others. All statistical tests were done with SPSS (SPSS Inc, Chicago, IL, USA).

Table 3.1 - *Summary of the medical records of each CVI and CN patient.*

ID	Age (yrs)	Group	Possible brain damage induced events	Intellectual and motor disability	Ophthalmologic disorders	
					Nystagmus	Other
1	2.4	CVI	NF	Y (motor)	Y	Strabismus
2	3.0	CVI	Small cerebral bleedings	N	Y	NF
3	3.6	CVI	Pre-eclampsia	N	Y	Strabismus
4	4.5	CVI	Hydrocephalus	Y (motor)	N	NF
5	4.9	CVI	Hemolytic hyperbilirubinemia	N	N	Cataract, strabismus
6	6.1	CVI	Intracerebral abscess, West syndrome	N	N	NF
7	7.9	CVI	NF	Y	N	Strabismus
8	9.5	CVI	HELLP-syndrome, hypoxic insult	N	N	NF
9	10.3	CVI	NF	Y	Y	NF
10	10.8	CVI	West syndrome	Y	N	Strabismus
11	11.0	CVI	Pre-eclampsia, hypoxic insult, IVH	Y	Y	NF
12	13.1	CVI	Scaphocephalie related increased ICP	Y	N	Opticoneuropathy, strabismus
13	5.3	CN	NF	N	Y	NF
14	6.0	CN	NF	N	Y	NF
15	6.3	CN	NF	N	Y	NF
16	6.8	CN	NF	N	Y	Strabismus
17	7.8	CN	NF	N	Y	Strabismus
18	7.9	CN	NF	N	Y	NF
19	8.3	CN	NF	N	Y	NF
20	9.2	CN	NF	N	Y	Cone dystrophy
21	9.4	CN	NF	N	Y	Cataract
22	9.4	CN	NF	N	Y	Oculomotor apraxia, rod dysfynction
23	9.5	CN	NF	N	Y	Cone/rod dysfunction

CVI= Cerebral Visual Impairment; CN= Congenital Nystagmus; NF= none found; Y= positive history; N= negative history; IVH= Intra ventricular haemorrhage.

Results

Gaze data were successfully measured in 28 children. In five participants, less than 5% of gaze data was measured because of poor tracking of the eyes that was not sufficient for further analysis. The medical records of these participants are summarized in table 3.1. Seven participants with CVI had an intellectual and/or motor disability and five were diagnosed with nystagmus. A frequently found associated ophthalmological disorder was strabismus. Two individuals in the comparison group did not complete the test and stopped during the session after approximately six minutes. None of the analyzed participants was born preterm. The top panel of figure 3.2 illustrates the orientating behavior (the solid line) of a 3-year-old typically developing child. At the onset of cartoon presentation in the upper right corner, the child's gaze was in the lower left corner. After detecting the cartoon, the child made an eye movement to fixate the cartoon. The middle panel shows the visual angle between the child's gaze and the location of the cartoon during each presentation. The RTF of each cartoon was defined as the time that the gaze was within 6° of the cartoon center. A cumulative plot of the RTF values was constructed and can be seen in the bottom panel of figure 3.2. An exponential function, fitted to the cumulative pattern, was used to derive RTF_{min} and RTF_{max}. In table 3.2, an overview of the ocular motor parameters is presented. In figure 3.3 (top panel), the RTF_{min} values are plotted against age. Significant differences in RTF_{min} and RTF_{max} values were found between the participants and the comparison group, but also between the group with CVI and the group with congenital nystagmus ($p<0.05$, Mann–Whitney U test). The RTF values were significantly longer in the group with CVI than in the group with congenital nystagmus. In the bottom panel of figure 3.3, a box–whisker representation of RTF_{min} values is presented for the 12 age-based subgroups of the comparison group and the adult group. Each box represents the 25th to 75th centile of the data. The band near the middle of the box is the 50th centile. The whiskers (or error bars) represent the 5th and 95th centiles of the data. The graph shows a gradual decrease in both values with increasing age. The mean RTF_{min} values measured in the comparison subgroup aged up to two years (mean 290 ms) were significantly higher than those measured in the comparison subgroup aged over four years (single asterisks; $p<0.001$, Bonferroni post-hoc testing). In the comparison subgroup aged over four years, the RTF_{min} was, on mean, 200 ms and in the adult group it was, on mean, 180 ms. The mean RTF_{max} values measured in the comparison subgroup aged below two years were significantly longer than the values measured in the comparison subgroup older than five years and in the adult group.

The top panel of figure 3.4 shows the variation of gaze fixation against age. Significant differences in GFA values were found between the group with CVI and the group with congenital nystagmus ($p<0.05$, Mann–Whitney U test). GFA values were significantly higher in the group with

congenital nystagmus (table 3.2). The bottom panel shows the box–whisker representations for the 12 age-based subgroups of the comparison group and for the adult group. In the comparison group, the GFA was on average 1.9°, which was equal to that assessed in the adult group. No statistically significant difference between age groups was found.

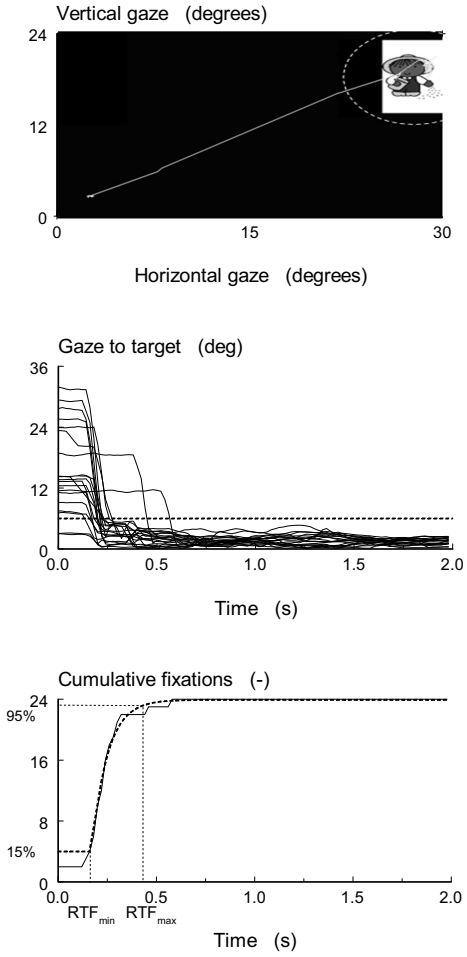


Figure 3.2 - *Cartoons were displayed in the corners of a remote eye-tracking monitor – see the top panel for an example. Superimposed is the orientating behavior (solid line) of a 3-year-old typically developing child, starting in the lower left corner and ending with steady cartoon fixation in the upper right corner. The middle panel shows the visual angles between gaze and cartoon positions against the first two seconds of all 24 cartoon presentations. The bottom panel shows the cumulative plot of the reaction times to fixation (RTF). The time that values exceeded 15% of the maximum values was defined as the minimum RTF (RTF_{min}). The maximum RTF (RTF_{max}) was defined as the time at which 95% of all cartoons were fixated.*

Table 3.2 *- Summary of the data of reaction time to fixation (RTF) and gaze fixation area (GFA) calculated from eye movement data in children with cerebral visual impairment (CVI) and individuals with congenital nystagmus (CN) and a comparison group aged between 0 and 12 years and adults.*

Group	n	mean age	RTF_{min} (ms) Mean (95% CI)	RTF_{max} (ms) Mean (95% CI)	GFA (deg) Mean (95% CI)
Participants					
CVI	12	7 y 3 mo	480 (340-620)	2740 (1450-4000)	2.6 (2.2-2.9)
CN	11	7 y 8 mo	390 (200-590)	1630 (190-3060)	3.2 (2.8-3.6)
Comparison group *					
0-1	11	7 mo	330 (260-400)	940 (820-1000)	2.0 (1.9-2.2)
1-2	21	1 y 6 mo	260 (240-270)	920 (740-1100)	1.9 (1.8-2.0)
2-3	21	2 y 4 mo	240 (220-250)	670 (600-750)	1.9 (1.8-2.0)
3-4	36	3 y 4 mo	220 (210-220)	640 (580-700)	1.8(1.8-1.9)
4-5	9	4 y 5 mo	210 (190-230)	600 (450-750)	1.7 (1.6-1.9)
5-6	18	5 y 5 mo	190 (180-200)	470 (400-550)	1.9 (1.8-1.9)
6-7	20	6 y 5 mo	190 (180-210)	480 (400-550)	1.9 (1.7-2.0)
7-8	16	7 y 3 mo	190 (180-200)	420 (360-480)	1.8 (1.7-1.9)
8-9	10	8 y 4 mo	190 (180-200)	400 (330-450)	1.7 (1.6-1.9)
9-10	13	9 y 3 mo	180 (170-200)	360 (300-430)	1.9 (1.7-2.1)
10-11	17	10 y 4 mo	180 (170-190)	430 (330-530)	1.9 (1.7-2.1)
11-12	22	11 y 7 mo	180 (170-190)	380 (340-410)	1.7 (1.6-1.8)
Adults	11	24 y 4 mo	180 (170-190)	390 (320-460)	1.9 (1.6-2.1)

** The comparison group was divided into 12 age-based subgroups, and an adult group. RTF_{min}= minimum reaction time to fixation; RTF_{max}= maximum reaction time to fixation; CI= confidence interval.*

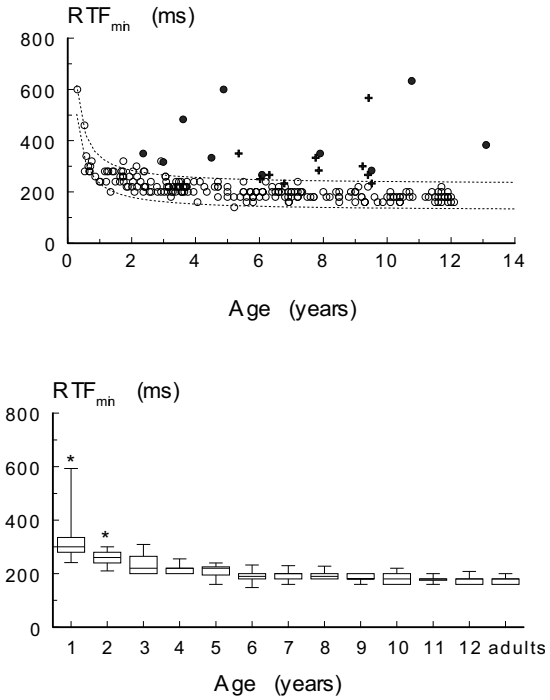


Figure 3.3 - *The top panel shows the minimum reaction time to fixation (RTF_{min}) of cartoons as a function of age for the participants with cerebral visual impairment (closed circles), the participants with congenital nystagmus (plus symbols), and the comparison group (open circles). The dotted lines represent the 95% confidence interval from the data of the comparison group. The bottom panel illustrates the box–whisker representations of the RTF_{min} values for the comparison group, separated into 12 age-based subgroups and the adult group. The RTF_{min} values of children up to the age of two years (indicated with an asterisk) were significantly longer compared with those of children older than four years and adults.*

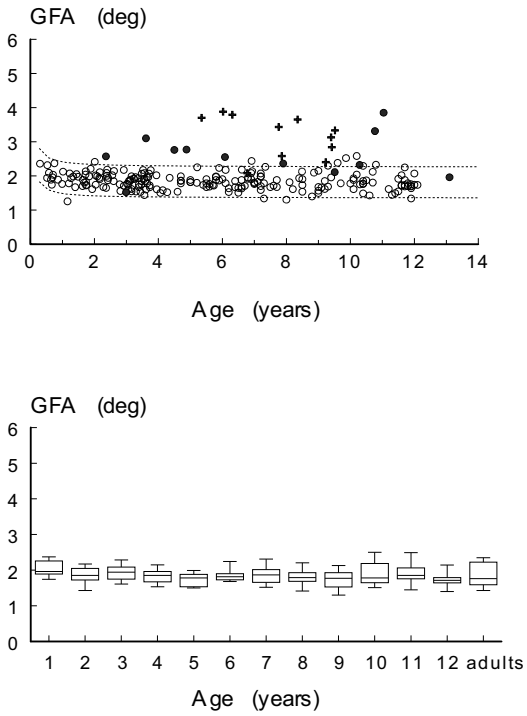


Figure 3.4 - *The top panel shows the performance of gaze fixation in terms of gaze fixation area was plotted as a function of age for the participants with cerebral visual impairment (closed circles), the patients with congenital nystagmus (plus symbols), and the comparison group (open circles).The dotted lines represent the 95% confidence interval from the data of the comparison group. In the bottom panel, these areas are presented as box–whisker plots for the comparison group and the adult group. No dependence was found between gaze fixation performance and age.*

Discussion

In the present study, orienting behavior was quantified on the basis of the RTF and GFAs of a new visual target. The longest delays in RTF_{min} values were found in the group with CVI. This finding supports the fact that visual processing time may be significantly prolonged in individuals with CVI. However, nystagmus is an eye movement disorder that also commonly occurs in individuals with CVI (Fazzi et al., 2007; Salati et al., 2002). Thus, RTF delays in the group with CVI could originate from either visual processing impairments or ocular motor instabilities. These instabilities were quantified and it was found that GFA values were only moderately increased in the group with CVI compared with the group with congenital nystagmus and the comparison group. Only two of the five individuals with CVI who also had nystagmus had GFA values in the range of the values

measured in individuals with congenital nystagmus. Based on the combination of RTF_{min} and GFA values, it appears that the delayed RTF_{min} values in the group with CVI are the result of impaired visual processing. Consequently, the RTF delays in individuals with congenital nystagmus may be the result of fixation instabilities, as GFA values were significantly highest in the group with congenital nystagmus. A critical factor is that individuals with CVI and individuals with congenital nystagmus often have reduced visual acuity (Fazzi et al., 2007; Hertle et al., 2002). Thus, quantification of orientating behavior in children with suspected various processing and/or motor disorders can be based on the presented remote eye-tracking technique. We plan to test and validate this methodology in a larger group of individuals with CVI or congenital nystagmus. A future aim would be to investigate whether individuals with CVI and nystagmus can be distinguished from individuals with congenital nystagmus at a young age, as suggested by the present data. Aspects of impaired processing need to be identified at a young age to optimize visual training. At present, no distinction is made between different disorders or symptoms in children with CVI. As a result, a wide range of visual impairments occur in CVI, among other deficits of visual perception and processing such as object recognition, spatial awareness, and altered stereopsis (Fazzi et al., 2007; Khetpal & Donahue, 2007).

Human ocular motor responses reflect cortical aspects of brain function. Recent work on activation of human ocular motor centers showed significantly increased latency of visual responses from the middle temporal region through the intra parietal sulcus to the frontal eye field (Sestieri et al., 2008). This indicates a feed forward recruitment of ocular motor cortical centers during the processing of visual information. The results suggest that these visuomotor processes, as well as motor responses, mature during the first three years of life. No significant difference was found between the older children and adults. The results of this study support the outcome of earlier studies on maturation of the visual and ocular motor systems (Canfield et al., 1997; Fukushima et al., 2000; Gredebäck et al., 2006; Yang et al., 2002). Previously, a rapid decline of saccade latencies was found during the first year of life (Canfield et al., 1997; Gredebäck et al., 2006), and a more gradual decline in saccade latencies was found in children aged over four years (Fukushima et al., 2000; Yang et al., 2002). Despite this gradual decline of saccade latency, the peak velocities of the saccades in 4-year-old children were not different from the values measured in adults (Fukushima et al., 2000). This last finding suggests maturation of the ocular motor system at the level of the brain before the age of four years. This is confirmed by the data from this study. Some small, but not significant, decline in RTF_{min} values were found in the comparison children who were aged between four and 12 years. The data from this study suggest that human visually guided ocular motor responses mature during the first three years of life and that target fixation stability is reached within the first six months of life.

This study is part of a larger study of visual behavior. Currently, measurements in the comparison group (i.e. typically developing children) are complete, but measurements in participants with CVI or nystagmus (i.e. children with visual processing and/or motor deficits) are still required before this large study is complete. The limitations of this research relate to possible bias in the comparison group, the quality of gaze data, and the total visual attention of a child. The children aged between four and 12 years were measured at one school. Here, the response was lowest. Written consent was received from the parents/caregivers of the children who were willing to participate. As medical ethical regulations did not allow for data collection from the non-responding group, some bias based on demographic differences cannot be excluded. The eye tracker had problems with tracking the eyes of five participants who wore glasses, which to some extent reduced the tracking quality of the machine. Each session lasted for approximately 12 minutes and included not only cartoons but also short films of form and motion coherence tests. From time to time the participants with CVI, in particular, exhibited reduced visual attention, resulting in a reduction in gaze data. Most of them, however, responded well to the cartoons, which were equally distributed throughout each session and seemed to improve visual attention. The differences found between RTF_{min} values in the present study and SRT values in previous studies may be attributed to differences in study methods, for example predictability of the target appearing or the type of visual targets. In our visually guided saccade task, the targets consisted of relatively large and high-contrast cartoons presented on a computer monitor. Normally, visual latency is related to the onset of saccades to targets using eye velocity and acceleration threshold criteria (Houben et al., 2006). Such an approach would have resulted in a reduction in the total number of trials that could be included for analysis, with around 40% being attributable to data gaps between the onset of presentation and the initiation of saccades. However, 70 to 90% of the trial data could be included for analysis on the basis of the timing of fixation of the cartoons. Even so, latencies based on fixations induce a bias between SRT and RTF_{min} values of around 60ms (Pel et al., 2010). Even if this bias is taken into account, the RTF_{min} values (approx. 210 ms in children aged 4y and approx. 180 ms in children aged 10–12y) were somewhat faster than the SRT values based on fixating small light-emitting diode lights in the dark (approx 450–500 ms in children aged 4y to approx. 200–250 ms in children aged 10y) (Fukushima et al., 2000). The authors believe that cartoons are a much more powerful visual stimulus than small light-emitting diode lights and conclude that presentation of relatively large cartoons improves target perception, recognition, and motor execution.

Acknowledgements

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4.

Quantification of visual orienting responses to coherent form and motion in typically developing children aged 0-12 years

Adapted from:

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Investigative Ophthalmology and Visual Science; 2012 (53) 2708-2714

Abstract

Background

Brain damage or brain development disorders can affect (the maturation of) visual processing functions, such as form and motion detection. The aim of our study was to investigate visual orienting responses of children to a coherent form and motion stimulus as a measure for maturation of visual information processing.

Method

The 213 typically developing children aged 0–12 years included in this study were shown a 100% coherent form and motion expansion stimulus on a remote eye tracking monitor. Orienting eye movements were quantified in terms of ocular motor reaction time to fixation (RTF). Children were divided in age groups and their performance was compared to 30 healthy adults with a mean age of 24.49 years (SD 3.62 years).

Results

The RTF values of coherent form in children up to six years old were significantly higher compared to the adult group ($P<0.05$, Dunnett post-hoc test). For motion, mature levels were reached at eight years old. RTF values depended on stimulus type ($F_{1, 168} =240.8$, $P<0.001$) and age ($F_{11, 168} = 25.8$, $P<0.001$), and there was a significant age by stimulus type interaction ($F_{11, 168} =2.2$, $P<0.05$).

Conclusion

Remote eye tracking may provide objective insight into the maturation of visual information processing of coherent form and motion without complex instructions or active cooperation. The quantification of typical visual orienting behavior in childhood may be used as a reference for children with brain dysfunction.

Introduction

Two classical cortical visual processing streams described in literature are: (1) the ventral stream, which connects the visual cortex with the temporal lobes, and (2) the dorsal stream, which connects the visual cortex with the parietal lobes. The ventral stream, often called the "what" pathway, involves visual processing functions, such as visual orientation, memory, and recognition of objects and faces. The dorsal stream, or "where" pathway, involves spatial cognition, motion sensitivity, simultaneous perception, and visual motor planning (Dutton, 2003; Ungerleider & Mishkin, 1982). It has been thought that form and motion processing can serve as indicators of the ventral and dorsal stream performance, respectively (Wattam-Bell et al., 2010). Form and motion processing have been assessed using psychophysical threshold detection methods. A visual stimulus is shown and repeated stepwise at different levels of coherence to determine thresholds of detection. Children must understand the task, and give a verbal or motor response to identify the presented target (e.g. pressing a button). This makes testing of very young children (<4 years) and children with an intellectual and/or motor disability almost impossible. In view of the postnatal maturation of the visual system, it would be best to detect dysfunctions as early as infancy to adjust daily support and improve individual rehabilitation.

Another method to study visual processing functions is measurement of eye movements during the presentation of visual stimuli. This relates to the behavioral discrimination task preferential looking (PL) (Fantz, 1965), in which visual stimuli induce reflexive eye movements to their target area when the visual information is processed by the brain. Quantifying visual orienting responses includes the integrity of the complete visual pathways (peripheral and central), and the ocular motor system (Noton & Stark, 1971a; Noton & Stark, 1971b; Yarbus, 1967). Impaired visual orienting responses may relate to an increased risk of higher visual processing dysfunctions, possibly in combination with ocular motor disorders. We developed a remote eye tracking method using this concept to quantify visual orienting behavior in children (Pel et al., 2011; Pel et al., 2010). A variety of stimuli is shown on the monitor, and gaze is measured without giving specific verbal instructions before the test or asking active cooperation. This means that young children (<4 years) and children with an intellectual disability can participate. One of the outcome measures that quantify visual processing is the ocular motor reaction time to a predefined target area of a stimulus.

Previous studies investigating form and motion processing using threshold detection methods show developmental trajectories that appear to depend on stimulus type. Gunn et al. used a coherent form stimulus, which consisted of tangentially oriented line segments, and showed that adult levels were reached at the age of 6–7 years (Gunn et al., 2002). Lewis et al. (2004) studied development of form processing using Glass patterns, and found that maturity was

reached between six and nine years of age. Directional motion discrimination was studied by Parrish et al. (2005) in children aged 3–12 years. In this study, the performance of a simple global motion perception task did not show significant improvement with age. A more complex motion detection task, in which coherently moving dots oscillated in opposite phase to those in the surrounding region, was studied by Gunn et al. (2002) and Spencer et al. (2000). They showed that coherent motion detection thresholds reached adult levels at 10–11 years. In conclusion, coherent motion processing seems to show a relatively slow delay in reaching adult levels compared to coherent form processing.

The aim of our study was to investigate if developmental trends exist in ocular motor reaction time to a 100% coherent form and a 100% coherent motion stimulus in typically developing children aged 0–12 years.

Population and Methods

Study population

We approached 460 typically developing children 0–12 years old in the region of Rijnmond, Rotterdam, The Netherlands. The children attended regular day care centers or primary schools. Parents were informed about the study by letter and 219 (48%) written consents were received. Children had normal or corrected-to-normal vision, and children with a history of developmental disorders or learning disabilities were excluded. At the time of measurement, three children were unable to attend and three children refused to participate on the day of measurement. This resulted in 213 children who were included in this study (115 females and 98 males, mean age 5.81 years, SD 3.47 years). The performance of the children was compared with a group of 30 healthy adults (18 females and 12 males, mean age 24.49 years, SD 3.62 years) to show mature levels for form and motion processing. A subgroup of 35 children (20 females and 15 males 1–9 years old, mean age 4.44 years, SD 2.32 years) was retested to assess test-retest reliability. The experimental procedures were approved by the Medical Ethical Committee of Erasmus University Medical Center, Rotterdam, The Netherlands (METC-2006-055). The study adhered to the Declaration of Helsinki for research involving human subjects.

Measurement setup and procedure

The setup consisted of a 17-inch monitor with an integrated infrared eye-tracking system (Tobii 1750, Tobii Corporation, Sweden). The eye tracker measured gaze position of each eye separately using cornea reflection at 50 Hz. The experiments were conducted in a quiet room at ambient light

conditions, and the monitor was positioned against a uniform background. Each child sat in a comfortable chair, at approximately 60 cm distance of the monitor to ensure efficient tracking of the eyes. The youngest children (4-12 months old) sat on a parent or investigator's lap. The system's latency was ±30 ms and it compensated free head movements, allowing a visual angle toward the monitor of 30° x 24° (1280 x 1024 pixels). In general, tracking of the eyes is influenced by tracking distance, pupil diameter and wearing glasses. First, a standardized 5-point calibration procedure of both eyes was performed. Next, one sequence of approximately 15 minutes was shown with the objective to present randomly visual stimuli. Each sequence contained smiley-like stimuli to test basic eye movements, such as saccades and pursuit, to exclude children with ocular motor apraxia. In addition, stimuli were shown to test visual orienting behavior and higher order visual processing functions, such as form and motion coherence, and competitive and non-competitive dots. Two different sequences were used for this study, both consisting of the same visual stimuli but presented in a different order.

All sequences shown to the 213 children included the form stimulus. Of these 213 sequences, 178 also included the motion stimulus. The stimuli contained a specific area with a higher salience, defined as the target area, which was presented in one of the quadrants of the monitor. The form stimulus consisted of an array of randomly orientated short white lines (0.2° x 0.6°, density 4.3 lines/degree^2) on a black background. In the target area, all the lines were orientated coherently to form a curved pattern (figure 4.1, left panel). The motion stimulus consisted of white dots (diameter 0.25°, density 2.6 dots/degree^2) that expanded over a black background, starting at the center of the target area and moving to the borders of the monitor (figure 4.1, right panel). This expansion had a velocity of 11.8 °/s and each dot had a limited life time of 0.4 seconds. At the viewing distance of 60 cm, the light intensity of the form and motion stimulus was 16 and nine lux, respectively. Both stimuli were repeated four times during the sequence (each time with the target area in another corner), and were shown for four seconds.

For the test-retest analysis, both sequences were presented to one child with a 10-minute break. For all 35 children within the subgroup, both shown sequences included the form stimulus. For 17 children within the subgroup, both sequences included the motion stimulus. The total testing time for children who participated in one sequence was 15 minutes. The total testing time for children who participated in test-retest analysis was approximately 40 minutes. All measurements were stored on the hard disk and analyzed manually off-line using self written Matlab programs (Mathworks Inc., Natick, MA).

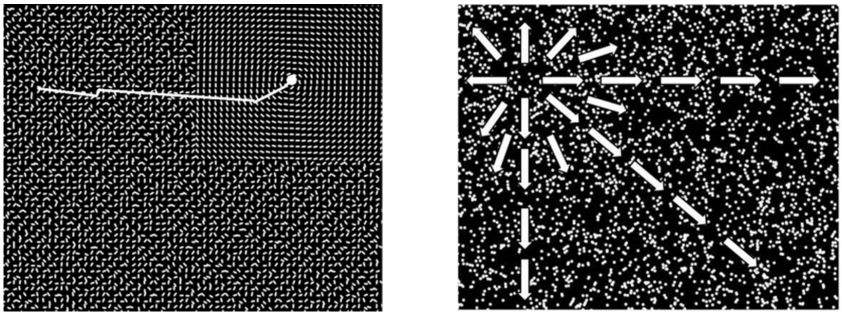

Figure 4.1 – *The visual stimuli. The 100% coherent form stimulus is shown in the left panel. In the upper right corner all the short white lines (0.2° x 0.6°, density 4.3 lines/degree²) are orientated coherently to form a curved pattern (target area). The thick white line represents the eye movement of a child. The child was fixating at the upper left corner at t=0, when the stimulus was shown, and made an eye movement to the target area in the upper right corner. The right panel shows the 100% coherent motion stimulus. The stimulus consisted of white dots (diameter 0.25°, density 2.6 dots/degree²) that expanded over a black background. In this example, the expansion originated from the upper left corner (target area). The white arrows illustrate the direction of the moving dots to the borders of the monitor. The expansion had a velocity of 11.8 °/s and each dot had a limited life time of 0.4 seconds.*

Data analysis and statistics

The eye tracker provided data of average viewing distance and gaze position on the monitor. To analyze gaze shifts to the predefined target area of the stimulus, gaze data were recalculated as a visual angle between gaze location and the center of the target area using the average viewing distance. The target area was a circle with a radius of eight degrees, and its center was identical to the center of the coherent form or coherent motion expansion in one quadrant. With an average viewing distance of 60 cm, the target area was approximately the size of one quadrant. For each stimulus presentation, the reaction time to fixation of the target area was defined as the time when the stimulus was shown on the monitor (t=0) until gaze was within eight degrees from the center of the target area, as illustrated in figure 4.2 (top panel). Based on chance, gaze already could be in the target area at t=0. These eye movements were excluded from analysis. The reaction time value was excluded from further analysis if, in the same measurement, (1) no gaze data were available in the first 500 ms, (2) the value was ≤120 ms, (3) more than three saccades were made to reach the target area, (4) duration of fixation before an eye movement was ≥1500 ms, or (5) the duration of fixation after reaching the target area was ≤200 ms. A cumulative plot was constructed of the available reaction time values (at least one, figure 4.2, bottom panel). An exponential curve was fitted to this cumulative plot to quantify the reaction time as the minimum reaction time (t_{min}) plus 1/3 of the time constant τ of the exponential curve. This value was denoted as the reaction time to fixation (RTF).

The children were divided in subgroups based on age (one year per group) to analyze the development over time and to compare different age groups with the adult group. To find age of

maturity, an ANOVA combined with Dunnett post-hoc testing was done on RTF values of the different age groups, with the adult group as the control group for both stimuli. In addition, a mixed ANOVA was done in those children who provided an RTF value for form as well as motion. Stimulus type was selected as the within-subject variable, and age group as a between-subject variable to verify maturation of orienting responses to coherent form and motion, and to verify stimulus type by age interaction. For the test-retest analysis the RTF value for the first and second sequence was labeled as RTF_1 and RTF_2, respectively. Reliability was calculated using the Intraclass Correlation Coefficient (ICC) of the RTF values, and this was confirmed with a Bland-Altman difference plot (Bland & Altman, 1999). All statistical analyses were performed in SPSS-17 (SPSS, Chicago, IL).

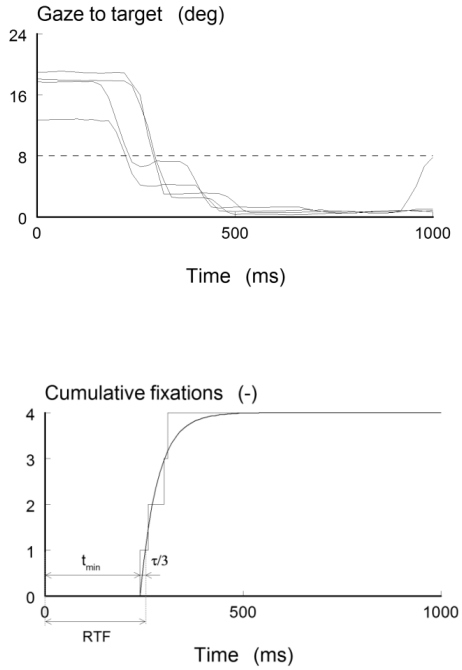

Figure 4.2 *- Data analysis. The top panel shows the visual angle between gaze and the center of the target area as a function of time. The reaction time was defined as the time when the stimulus was shown on the monitor (t=0) until gaze to the target area first crossed the dotted line (within eight degrees). Because each stimulus was repeated four times, four gaze lines are shown in this figure, and resulted in reaction time values. Note that the duration of presentation is 4.0 seconds. We plotted the first 1.0 second for illustration purpose only. The bottom panel shows a cumulative plot of the reaction time values. An exponential curve was fitted to this cumulative plot to quantify the RTF, which was the minimum reaction time (t_{min}) plus 1/3 of the time constant τ of the exponential curve.*

Results

Form

In eight of the 213 children no reaction time values were available, or were excluded from further analysis based on the criteria as mentioned in the Materials and Methods section. As a result, in 205 children (96%) the RTF was calculated successfully for form coherence. The majority of insufficient measurements were due to failure of eye tracking, either caused by glasses of a child or a lack of attention. The mean RTF per age group is summarized in table 4.1. Figure 4.3 (top panel) illustrates the RTF values of the form stimulus against the age of the children. The ANOVA revealed that age contributed significantly to the decline of RTF values ($F_{12,222}$ = 47.8, P<0.001). The Dunnett post-hoc test showed significant higher RTF values in the age groups 0 to 5 compared to the adult group (P<0.05), indicating that adult levels were reached at the age of six years. One of the 35 children, who participated in the test-retest analysis, was excluded from analysis, since only one RTF value was available for the form stimulus. Of both sequences shown to the 34 children, a mean of 71% (SD 21%) and 69% (SD 18%) gaze data were measured during the first and second sequences, respectively. The ICC was 0.79 with a 95% confidence interval of 0.58 to 0.89 (P<0.001), indicating an excellent reliability (Cicchetti & Sparrow, 1981). This was confirmed with a Bland-Altman difference plot (Bland & Altman, 1999), showing an average difference of 38 (SD 132) ms.

Motion

During the presentation of the motion stimulus, 156 children (88%) showed successful gaze data. In 22 children the reaction time values were excluded, mainly due to pursuit-like eye movements with a duration of 1500 ms or longer. The mean RTF per age group is summarized in table 4.1. Figure 4.3 (middle panel) illustrates the RTF values against age. Again, the ANOVA revealed that age contributed significantly to the decline in RTF values ($F_{12,170}$=11.4, P<0.001). Here, we found that the RTF values of the children until seven years old were significantly higher compared to the adult group (P<0.05, Dunnett posthoc test). For motion expansion processing, age of maturity was found at eight years old. For the test-retest analysis of motion, nine of the 17 children had only one RTF value. Of the sequences shown to the remaining eight children, means of 86% (SD 12%) and 86% (SD 14%) gaze data were measured during the first and second sequences, respectively. The reliability analysis of the RTF showed an ICC of 0.89 with a 95% confidence interval of 0.45 to 0.98 (P<0.01). Although this result indicates an excellent reliability (Cicchetti & Sparrow, 1981), we emphasize that this analysis was based on only eight test-retest observations. Given this low number, the test-retest reliability with current data has limited meaning.

A subgroup of 180 children provided an RTF value for form and motion. A mixed ANOVA applied in this group confirmed that RTF values depended significantly on stimulus type ($F_{1,168}$=240.8, P<0.001) and age ($F_{11,168}$ =25.8, P<0.001), and that the age by stimulus type interaction was statistically significant ($F_{11,168}$ =2.2, P<0.05). Figure 4.3 (bottom panel) shows for this subgroup the mean RTF values and SD to illustrate maturation over time for both stimuli (P<0.05, Dunnett post-hoc test). The asterisks illustrate those age groups with significantly higher RTF values compared to the adult group.

Table 4.1 - *Summary of Orienting Responses to the 100% Coherent Form and Motion Stimulus. Subgroups are based on age, which resulted in 13 age groups, including the adult group. Presented for each age group are the number of children (n), mean age, and the RTF values. We found decreasing RTF values for the form and motion stimulus.*

GROUP		**FORM Mean (SD)**			**MOTION Mean (SD)**		
		n	**Age (y)**	**RTF (ms)**	**n**	**Age (y)**	**RTF (ms)**
0	0-1 y	5	0.72(0.26)	901(315)	2	0.61 (0.11)	915 (368)
1	1-2 y	20	1.54 (0.27)	789 (185)	10	1.66 (0.17)	1075 (447)
2	2-3 y	21	2.41 (0.29)	686 (185)	7	2.37 (0.26)	1030 (298)
3	3-4 y	35	3.44 (0.26)	544 (133)	20	3.50 (0.26)	803 (421)
4	4-5 y	10	4.52 (0.29)	488 (164)	8	4.56 (0.27)	853 (235)
5	5-6 y	18	5.56 (0.30)	399 (79)	14	5.54 (0.31)	672 (213)
6	6-7 y	20	6.60 (0.29)	327 (42)	20	6.60 (0.29)	593 (122)
7	7-8 y	15	7.32 (0.23)	328 (48)	15	7.32 (0.23)	614 (156)
8	8-9 y	10	8.45 (0.28)	326 (51)	9	8.45 (0.30)	567 (64)
9	9-10 y	14	9.35 (0.33)	306 (41)	13	9.31 (0.30)	540 (153)
10	10-11 y	15	10.42 (0.24)	292 (33)	16	10.42 (0.23)	543 (85)
11	11-12 y	22	11.72 (0.23)	277 (41)	22	11.72 (0.23)	474 (58)
20	Adult	30	24.49 (3.62)	295 (53)	27	24.62 (3.78)	399 (89)

Figure 4.3 - *RTF values as a function of age. Top panel: 100% coherent form stimulus. The dotted line represents a power curve estimation of all RTF values using regression analysis. The fitted equation is* $y=928x^{-0.497}$*. Middle panel: 100% coherent motion stimulus with a power curve estimation. The fitted equation is* $y=1153x^{-0.343}$*. Bottom panel: The mean RTF and standard deviations of the form (grey) and motion (black) stimulus per age group. The age groups in this figure include only those children who had available data for both stimuli. *The age groups that showed significant higher RTF values compared to the adult group (P<0.05, Dunnett post-hoc test).*

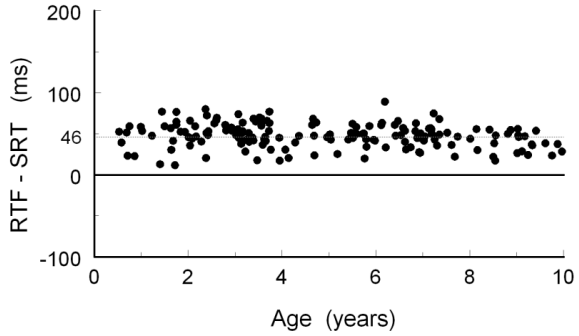

Figure 4.4 - *The difference between RTF and SRT is plotted as a function of age. An average difference of 46 (SD 15) ms existed between saccade onset and cartoon fixation. No age-related changes in eye movement control were found in typically developing children 0–12 years old.*

Discussion

To study form and motion processing, orienting eye movements in response to a coherent form and motion stimulus were quantified in terms of ocular motor reaction time to fixation (RTF). We found that the RTF of the coherent form stimulus developed until the age of six years, and of the coherent motion stimulus until eight years. Our results suggested that maturation of coherent form and motion processing follow different timelines. This difference in trajectory of development is comparable to the outcome of other studies using psychophysical threshold detection methods (Gunn et al., 2002; Lewis et al., 2004; Spencer et al., 2000). The study of Gunn et al. (2002) showed that form processing reached adult levels at an earlier age compared to motion processing. Still, the age of maturation for form and motion processing found by previous studies may differ from our study. This difference may be explained by the difference in methods applied: (1) our method is based on the reaction time as an outcome measure, while other studies present threshold levels; (2) our method analyzed only 100% coherent stimuli, while threshold detection methods use different levels of coherence to determine the development of visual processing; and (3) our method does not include perception. Orienting eye responses are induced reflexively toward visual stimuli when its information is processed by the brain. At this level of visual processing, the perception, that is to understand what is seen and give verbal responses, like in psychophysical threshold methods, might not even be completed yet. In a future study, it would be interesting to test ocular motor reaction times to fixation as a function of decreasing coherent threshold levels. It might be that the age of maturation is different for levels of coherence.

Recent studies reported that the relative maturation of form processing is stimulus dependent. The 4-5.5 month-old infants showed relatively strong sensitivity to line patterns, compared to a limited sensitivity to conventional Glass patterns. Moreover, sensitivity to patterns depended on the length of the local line segments (Palomares et al., 2010). Lewis et al. (2004) found that for each type of Glass pattern used, thresholds for 9-year-olds were no different than those of adults. However, for all ages, thresholds were significantly worse for patterns with parallel structure than for patterns with concentric structure. We acknowledge that the presented developmental timelines must be placed in context with the coherent form and motion stimulus used.

As stated, visual orienting responses reflect visual processing, including ocular motor control. It might be that reduction of reaction times to fixation relates to maturation of eye movement control. Often the onset of eye movements, the so-called saccadic reaction time (SRT), is used as a measure for visual processing time. In a previous study, we compared the RTF values to a cartoon stimulus with their corresponding SRT values in a subgroup of the children presented in the current study (Pel et al., 2010). SRT values were derived from the moment that eye velocity of the saccade toward the target area of the cartoon exceeded 50 °/s. The difference between RTF and SRT, the duration of the eye movement, can be regarded as a measure for eye movement control. We applied a similar approach for the complete group of children, and constructed a Bland-Altman difference plot against age (figure 4.4). On average, it lasted 46 (SD 15) ms between the onset of the eye movement and reaching the target area. Based on ANOVA, no age-related changes in eye movement control were found in the typically developing children between 0 and 12 years old. This suggests a fixed duration for eye movement control in RTF values. Note that the sample frequency of 50 Hz is rather low to calculate SRT values accurately and we found better repeatability for RTF values compared to SRT values. For this reason, we preferred to analyze orienting responses in terms of reaction times to fixations. We concluded that remote eye tracking is well suited to assess the ocular motor reaction time to fixation during visual orienting behavior tasks (Pel et al., 2010).

The relatively late maturation of using motion information in orienting behavior seems paradoxical to the organization of this visual pathway in the brain. Motion is processed through the fast conducting magnocellular layers, via the lateral geniculate nucleus (LGN), toward the visual cortex. This is in contrast with form, which is processed mainly via the parvocellular layers with slower conduction velocities (Livingstone & Hubel, 1988). The processing pathways of form and motion beyond the visual cortex may go through reorganization between infancy and adulthood (Wattam-Bell et al., 2010). Recent theories on visual attention argue that the brain constructs an internal saliency map based on features, such as color, form, and movement (Koch & Ullman, 1985; Treue, 2003). We compared RTF data of the form and motion stimulus with earlier obtained data using a colored cartoon stimulus within the same group of children (Pel et al.,

2011). Figure 4.5 illustrates that children have the fastest RTF to the cartoons, followed by form and then motion. An explanation may be offered by differences in saliency between the visual stimuli. The cartoon stimulus had the highest contrast to its background, had colors, and moved with modest speed up and down. The combination of these visual aspects presumably increased its saliency over that of form and motion alone. In addition, processing of motion expansion, presented in a random array of dots, requires local information on dot speed, size, density, luminance and direction. This integration of information might reduce the saliency of the motion stimulus compared to the form stimulus. Future studies should analyze the impact of saliency on the reaction time to fixation, and on age of maturation by including stimuli that vary in visual aspects. However, many intrinsic and extrinsic aspects can influence processing time. With current knowledge, we do not know to what extent each aspect influences this process from retinal input to ocular motor output.

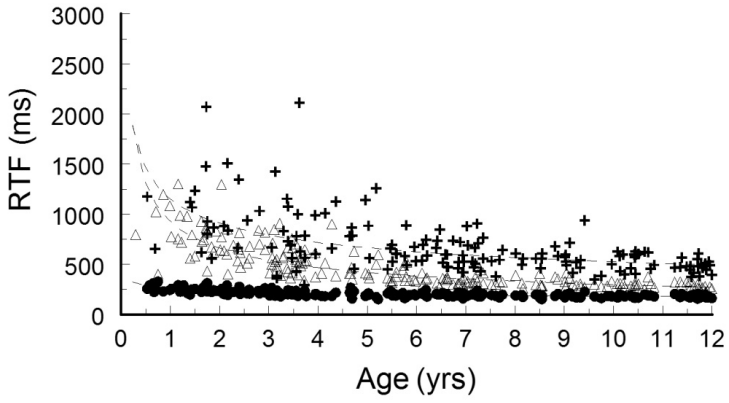

Figure 4.5 - *The RTF of the motion (plus symbols), form (open triangles) and cartoon (closed circles) stimulus as a function of age. The lines represent a power curve estimation per stimulus of all RTF values using regression analysis. This figure illustrates that orienting responses to cartoons were on average fastest, followed by form and, finally, motion.*

A main distinctive feature of our study is based on the applicability of the remote eye tracking method. Children of all ages, from approximately four months old, can participate. Since no instructions, assignments, or verbal responses are necessary. Eye-hand related demands, such as pressing a button, are avoided and the method compensates for free head movements. This means that children with motor disabilities are expected to be able to perform the task as well. The duration of the measurement is relatively short (15 minutes), the method is non-invasive, and

has a low burden for children. Since the equipment is portable, the measurements can be performed at schools or at other surroundings familiar for the child. These advantages resulted in a relatively large group of children 0–12 years old who were included for this study.

For clinical application, the limitations of the method applied in our study relate to the small number of repetitions per stimulus type and the visual behavior of a participant. The emphasis of our study is on group behavior across an age spectrum between 0 and 12 years. This large group of children did show missing gaze data to coherent stimuli, with the consequence that RTF values could not be calculated. For clinical testing, we would increase the number of repetitions per coherent stimulus to at least eight (for form as well as motion) to improve the success rate of a measurement. The application of cartoon stimuli that were distributed equally in each trial seemed to retain visual attention. Still, some children did show reduced visual attention at the onset of the stimulus, which resulted in loss of the first reflexive orienting responses. If no gaze data were available within the first 500 ms after presentation of the stimulus, this part of gaze signal was not included for calculating an RTF value. When data were missing for a longer period of time, one cannot exclude the possibility that during such data gaps, an eye movement already was made. The consequence was, for example when 450 ms gaze data were missing, that this time was added up to the total reaction time to fixation. This may affect the spread of the data, however, to a limited extent. We found a rather low percentage of orienting responses that missed part of the first 500 ms of gaze data. These gaps mostly were the result of eye blinking or a lack of visual attention, meaning that a child simply was not looking at the monitor during the presentation of a stimulus. The majority of gaze data gaps was at the end of a stimulus presentation and resulted from a lack of visual attention. Occasionally, the eye tracker had problems with detecting the eyes of children who wore glasses. This also reduced tracking quality. To overcome some of the stated limitations, we are developing and testing a more interactive measurement setup. Such a system includes real-time decision criteria to quantify objectively whether a first reflexive orienting response to a cartoon or a coherent stimulus was measured successfully.

We believe that the quantification of typical orienting behavior in childhood represents a reference of neurological development. Future studies may assess abnormal development and diagnosis of visual processing dysfunctions in a case control experiment. One group that has our special attention includes children with a high risk of having visual processing dysfunctions, possibly combined with ocular motor disorders due to brain damage or brain development disorders. This includes children with developmental and/or intellectual disabilities in general, or children with a specific etiology, such as cerebral palsy, periventricular leukomalacia, prematurity, and hydrocephalus. Another case group includes children diagnosed with a loss of visual function without damage to the ocular structures, which is labeled commonly as cerebral visual impairment (CVI). CVI currently is a very broad diagnosis of exclusion and based on anatomical landmarks. A

separate description of the types of visual dysfunctions can be useful and a good addition to clinical practice (Boot et al., 2010). Future studies may focus on the correlations between abnormal visual orienting responses and the type of brain damage, and to dissociate the abnormal orienting responses from ocular motor disorders.

Conclusion

Visual orienting responses to coherent form and motion stimuli were quantified in typically developing children aged 0–12 years without complex instructions or active cooperation. The ocular motor reaction times to fixation must be placed in context with the stimuli used, but the results confirm that coherent form processing reaches adult levels at an earlier age than coherent motion processing. The remote eye tracker may be a potentially good method for testing visual information processing in childhood. The method can give us objective and reliable insight into the visual behavior of young children.

Acknowledgments

We thank the children, their parents, the schools, and daycare centers for their cooperation.

5.

Delayed visual orienting responses in children with developmental and/or intellectual disabilities

Adapted from:

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Abstract

Background

Assessment of higher visual processing functions mostly requires active cooperation of participants, which is problematic in children with intellectual disabilities (ID). To circumvent this, we applied remote eye tracking to quantify (ab)normal visual orienting responses in children with ID in terms of reaction times to visual stimuli.

Method

We presented visual stimuli (cartoon, coherent form and coherent motion) to 127 children (2-14 years) with developmental and/or ID (risk group) and simultaneously measured their orienting ocular motor responses. Reaction times to fixation (RTF) in the risk group were compared to RTF values of an age-matched control group.

Results

Overall, in 72% of the children in the risk group, RTF values to cartoon were delayed, in 47% to form, and in 38% to motion. The presence of delayed reaction times was highest in the group of children >4 years with ID.

Conclusion

Our data show that a majority of children with developmental and/or ID have delayed visual orienting responses. This suggests that this group has increased risk for higher visual processing dysfunctions. Future studies are planned to relate abnormal orienting responses to type of brain damage and to dissociate the responses from ocular motor disorders.

Introduction

Individuals with intellectual disabilities (ID) have an increased prevalence of visual impairment which is related to a low IQ (Sandfeld Nielsen et al., 2007; van Splunder et al., 2006; Warburg, 2001). In children with an IQ <80 aged 4-15 years, Sandfeld Nielsen et al. (2007) found a prevalence of visual impairment (acuity <6/18) of 10.5%. In the subgroup of children with an IQ <50, the prevalence was increased to 22.4%. These percentages are much higher compared to the general children's population of high-income countries, where approximately 0.1% of the children have a visual impairment or blindness (Bhasin et al., 2006; Cans et al., 2003). Pre- and perinatal brain damage or brain development disorders are the main causes for visual impairment in children with ID (Kwok et al., 1996; Sandfeld Nielsen et al., 2007). Low visual acuity and visual field defects may be explained by damage to primary visual pathways. However, brain damage or brain development disorders may also affect higher visual processing functions, such as form recognition, motion detection, or spatial orientation. Higher visual processing functions can be affected in the presence of normal acuity, and thus can easily be missed (Dutton & Jacobson, 2001; Edmond & Foroozan, 2006; Fazzi et al., 2009). Because visual impairment can profoundly influence psychosocial development, daily functioning, and school achievement, it is important to screen for impairments at an early age (<4 years). Studies investigating visual impairment in children with ID often exclude very young children and mostly address low visual acuity and visual field defects as only outcome parameters. Neuropsychological and observational tests, which are currently the methods used to assess higher visual processing functions, are difficult to perform in this group, due to a lack of understanding and cooperation. The consequence is that visual impairment including higher visual processing dysfunctions in children with ID is highly under diagnosed. Support for this is given by Stiers and colleagues, who studied visual perceptual functioning within a risk group of 96 physically disabled children (68 with cerebral palsy), aged 4-21 years, of which 91% had an IQ <85. In this study, 37.5% of the children showed impairment on at least one visual perceptual task, based on a score at or below the 5th percentile of children without disabilities (Stiers et al., 2002). In addition, it has been reported that certain developmental disorders affect specific visual processing dysfunctions. For example, fragile-X syndrome and Williams syndrome are associated with difficulties in visual spatial cognition (Grinter et al., 2010).

In the current study we measured visual orienting responses in children with ID using a remote eye tracker. The method aims at measurement of the first reflexive orienting response towards the appearance of a visual stimulus presented on the eye tracker's monitor. With quantification of visual orienting responses, one tests the integrity of the complete visual processing pathways and the ocular motor system (Noton & Stark, 1971a; Noton & Stark, 1971b;

Yarbus, 1967). Impaired visual orienting responses may relate to an increased risk of higher visual processing dysfunctions, possibly in combination with ocular motor disorders. The concept of measuring visual orienting responses is based on the behavioral discrimination task preferential looking (PL) (Fantz, 1965; Sturm et al., 2011). In the PL task, visual stimuli induce reflexive eye movements to a target area, following processing of the visual information by the brain. Human infants prefer to fixate patterned surfaces more than homogeneous ones and respond to visual stimuli by moving their eyes in the direction of the object of visual interest (Sturm et al., 2011). PL has been applied frequently in the research field as well as in daily practice to establish threshold values for, amongst others, visual acuity, color vision, contrast sensitivity, face recognition, and depth cues (Kavsek et al. 2012; Kobayashi et al., 2012; Sturm et al., 2011). The use of a remote eye tracking system to monitor eye movements provides an efficient way to present visual stimuli and allows the quantification of visual orienting responses. As the technique requires no specific verbal instructions or active cooperation (e.g. pressing a response button), young children (from approx. four months old) and children with ID can participate. The aim of the current study was to quantify in a group of children with developmental and/or ID (risk group) the number with delayed visual orienting responses to one or more of three different stimuli in comparison to an age-related control group. We selected cartoons to test general visual attention and visual orienting behavior. It has been suggested that form and motion processing can serve as indicators of (ab)normal ventral and dorsal stream performance (Wattam-Bell et al., 2010). The ventral stream, often called the "what" pathway, involves visual processing functions such as visual orientation, memory, and recognition of objects and faces. The dorsal stream, or "where" pathway, involves spatial cognition, motion sensitivity, simultaneous perception, and visual motor planning (Ungerleider & Mishkin, 1982; Dutton, 2003). Therefore, we chose coherent form and motion stimuli to selectively test impairment of either visual information processing stream.

Methods

Study population

The risk group included children with a developmental and/or ID, aged 2-14 years, in the Rotterdam and Leiden regions of The Netherlands. Children aged 2-4 years were approached through rehabilitation centers, where they attended special therapeutic preschool groups. All children were diagnosed with a developmental disability by the physiatrist of the rehabilitation center. Children aged 4-14 years were approached through two types of schools for special education in The Netherlands. The first type of school was designed for children with a multiple disability, including an IQ <70 in combination with a motor disability. The second type of school

educated children with mainly an ID in an IQ range of 20 to 70. In total, the parents of 302 children were informed about the study by letter. After informed consent, information on visual acuity and IQ was retrieved from medical records. IQ was labeled according to ICD-10 (International Classification of Disease): mild ID if IQ ranges between 50-69, moderate ID if IQ ranges between 35-49, severe ID if IQ ranges between 20-34, and profound ID if IQ is below 20. At the time of measurement, all children were screened for abnormal acuity using visual acuity cards (Teller acuity cards or Lea Hyvärinen single symbols acuity cards at 3 m). Children with an acuity <0.1 (10%; LogMAR 1.00; Snellen 20/200) were excluded from this study. If screening failed, we used visual acuity found in medical records that was assessed at an earlier stage by a physician or optometrist. Children with ocular motor apraxia were excluded. The data of the risk group were compared with reference values obtained from a control group of 213 children aged 0-12 years (115 females and 98 males, 5.81 (3.47) years, mean (SD)) in the region Rijnmond, Rotterdam, The Netherlands (Pel et al., 2011). These children attended regular day care centers or primary schools, had normal or corrected-to-normal vision and did not have a history of developmental disorders or ID. The experimental procedures were approved by the Medical Ethical Committee of Erasmus University Medical Center, Rotterdam, The Netherlands (METC-2006-055). The study adhered to the Declaration of Helsinki for research involving human subjects.

Measurement setup and procedure

The setup consisted of a 24-inch monitor with an integrated infrared eye-tracking system (Tobii T60XL, Tobii Corporation, Sweden). The eye-tracker measured gaze position of each eye separately using cornea reflection at 60 Hz. The experiments were conducted in a quiet room at ambient light conditions and the monitor was positioned against a uniform background. The children sat on a parent or investigator's lap, in a comfortable chair, or in their own wheelchair at 60 cm distance in front of the monitor. The system's latency was ±30 ms and it compensated free head-movements, allowing a visual angle towards the monitor of 30° x 24° (1280 x 1024 pixels). First, a standardized 5-point calibration procedure of both eyes was performed. Next, one sequence of ~15 min. was shown with the objective to randomly present short movies (visual stimuli) for testing basic eye movements, such as fixation and pursuit, and also movies to test (higher order) visual processing of e.g. form and motion. All stimuli were shown four times during the sequence. These tasks were interspersed with the cartoons, in total 24, initially to improve visual attention of a child towards the monitor. However, it became clear that gaze responses to cartoons provided valuable information about orienting responses and we decided to include this stimulus for further analysis as well. Two different sequences were used for this study, both consisted of the same visual stimuli but presented in a different order.

All stimuli contained a specific area in one of the quadrants of the monitor, defined as the target area (see figure 5.1). The target area of the form and motion stimulus with a visual angle of eight degrees covered about one quadrant. The target area of the cartoon stimulus, being presented more to the edge of the monitor, covered only a part of one quadrant and had a visual angle of six degrees. The cartoons were selected from a collection by Dick Bruna (creator of Miffy the rabbit). Each cartoon was presented on a uniform black background and had a visual angle of 4.5° x 9.0° (width x height). The cartoon moved at a constant speed up and down (V= 3°/s; A= 1.5°). In total, six cartoons were shown per quadrant, each with a duration of 10 seconds. The coherent form stimulus consisted of an array of randomly oriented short white lines (0.2° x 0.6°; density 4.3 lines/degree²) on a black background. In the target area, all the lines were oriented coherently to form a curved pattern. The coherent motion stimulus consisted of expanding white dots (diameter 0.25°; density 2.6 dots/degree²) against a black background. The dots started at the center of the target area and moved to the borders of the monitor (V= 11.8°/s; limited life time 0.4 s). Each time, the form and motion stimulus were presented with the target area in another quadrant and were shown for four seconds. At the viewing distance of 60 cm, the light intensity of the form, motion, and cartoon stimulus was 16, nine and six lux respectively. All measurements were stored on the hard disk and manually analyzed off-line using self-written Matlab programs (Mathworks Inc., Natick, MA, USA).

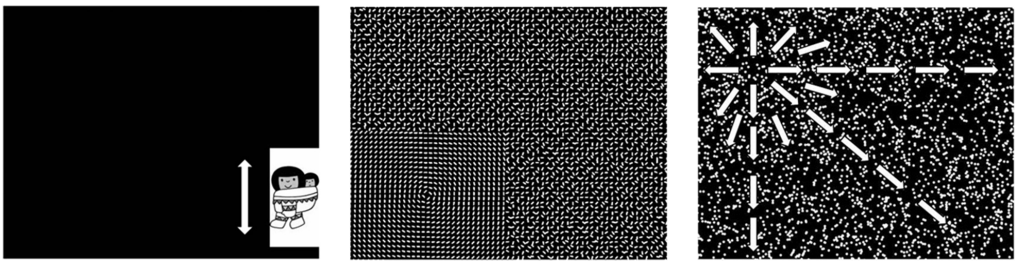

Figure 5.1 - *Three different stimuli were displayed on the remote eye tracking monitor and analyzed in this study, denoted as the cartoon, the form, and the motion stimulus. The target area of the cartoon stimulus was a colored cartoon which moved with modest speed up and down. An example is shown at the left panel. The cartoons were reproduced with permission, copyright Mercis BV, Amsterdam, The Netherlands. The form stimulus consisted of short white lines which were coherently oriented to form a curved pattern in one quadrant of the monitor, see middle panel. The motion stimulus consisted of expanding white dots for which the direction is illustrated using white arrows in the right panel.*

Data analysis and statistics

Gaze data were expressed as a visual angle between the gaze location and the center of the target area. For each stimulus presentation, reaction time was defined as the time when the stimulus was shown on the monitor (t=0 s) until gaze was within the target area. This value was excluded from further analysis if, in the same measurement, (1) no gaze data were available in the first 500 ms, (2) the value was ≤120 ms, (3) more than three saccades were made to reach the target area, (4) duration of fixation prior to an eye movement was ≥1500 ms, or (5) the duration of fixation after reaching the target area was ≤200 ms. At least one successful value had to be available to determine the minimum reaction time: the Reaction Time to Fixation (RTF). Figure 5.2, top panel, illustrates orienting gaze (white line) at the onset of a form coherence stimulus. Gaze started in the upper left corner. After detection of the form in the upper right corner, denoted as the target area, the subject made an eye movement towards the center of the target area. Data analysis started with the calculation of the visual angles between gaze point and target center point of all four form stimulus presentations, see the middle panel. Note that the duration of presentation is at least 4.0 s. We plotted the first 1.0 s for illustration purpose only. The dashed line in this panel illustrates the border of the target area that was set for the form stimulus at eight degrees. A cumulative plot was constructed from the time values at which gaze crossed this eight degrees border of the target area, see bottom panel. An exponential curve was fitted to this cumulative plot to quantify the average reaction time to the target areas:

$$CF(t) = CF_{max} * \{1 - \exp(t_{min} - t) / \tau\} \qquad \text{(eq. 1)}$$

With $CF(t)$ = cumulative number of fixations as a function of time (-)

CF_{max} = maximum number of fixations (-)

t_{min} = fastest reaction time crossing the target area border (s)

τ = time constant (s)

The unknown parameter in equation 1 is the time constant τ. This time constant reflects the time needed to reach ~66% of the maximum number of the cumulative fixations (CF_{max}) per subject. We defined the RTF as t_{min} plus 1/3 of the time constant τ to ensure that RTF described the timing of reflexive target fixations, see figure 5.2, bottom panel. This procedure was similar for obtaining RTF values of cartoon and motion coherence stimuli. Figure 5.3 illustrates the RTF values to form coherence stimuli in the control group plotted as function of age. All RTF data assessed in this group served to establish areas of reference, so-called reference percentiles. Age-related reference percentiles were constructed according to Altman (Altman, 1993). The RTF is assumed to follow a normal distribution for a given age between 0-12 years old. First, the mean RTF was modeled as a function of age using a (non-linear) exponential function, see figure 5.3, top panel. Next, absolute residuals were regressed on age with a similar non-linear exponential function to provide an

estimate of the standard deviation of the RTF as a function of age. Means and standard deviations were combined to give estimates for the reference percentiles, see figure 5.3, bottom panel. This procedure was similar for obtaining age-related reference percentiles for the cartoon and the coherent motion stimuli.

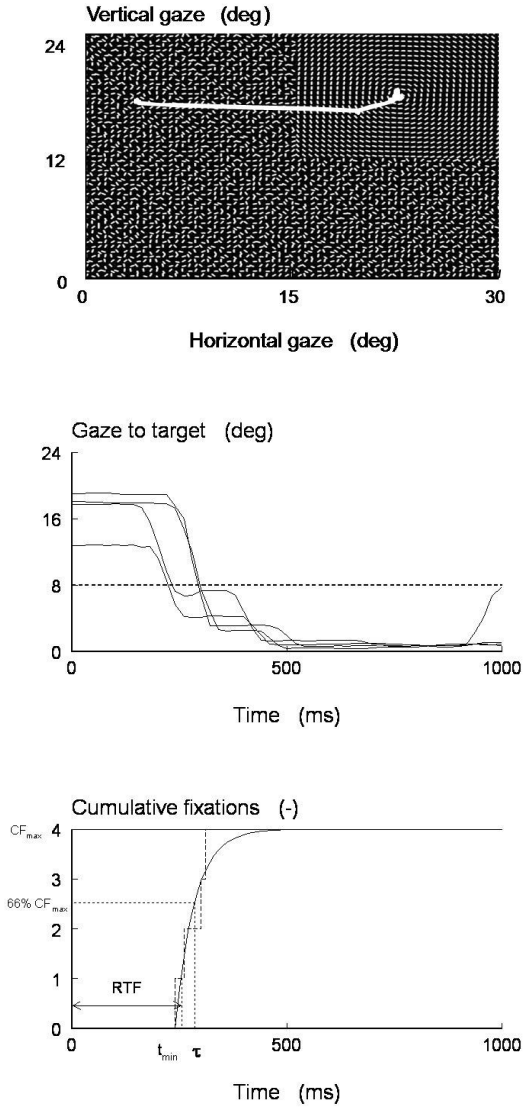

Figure 5.2 - *The top panel shows gaze of a subject on the eye tracker monitor at the onset of a form coherence stimulus presentation. The middle panel shows the visual angles between gaze and center of the target area positions against the first second of all four form stimuli shown. The bottom panel shows the cumulative plot of the time values that gaze crossed an eight degrees border (dashed line) of the target area. An exponential curve was fitted to this cumulative plot to quantify the Reaction Times to Fixation (RTF).*

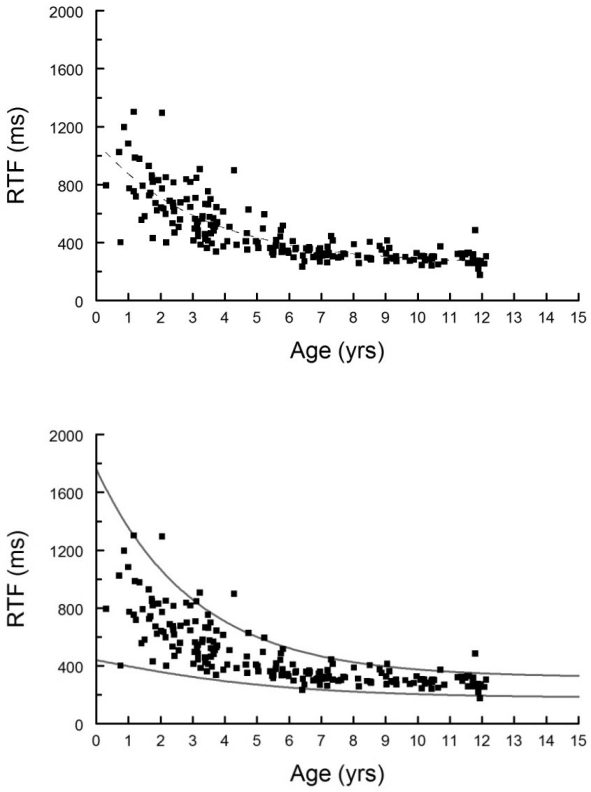

Figure 5.3 - *In the top panel, RTF values of the control group to the form stimulus are plotted against age. An age related reference area was constructed using a two-step procedure. First, the mean RTF was modeled as a function of age using a (non-linear) exponential function, illustrated by the dashed line. Next, the absolute residuals were regressed using the same non-linear function. The borders of the age-related reference area are the upper and lower limit of the reference percentiles, illustrated by the two straight lines in the bottom panel.*

The RTF values of the risk group were compared with the age-related reference percentile, i.e. the reference area. If a child had an RTF value above the upper border of the reference area, the RTF was classified as a delayed reaction time to fixation. Reliability of RTF assessment was calculated for each stimulus in a subgroup of 35 children of the control group (20 females and 15 males between 1-9 years old, 4.44 (2.32) years, mean (SD)), using the Intraclass Correlation Coefficient (ICC). The ICC was 0.84, 0.75, and 0.70 for the cartoon, form, and motion stimulus respectively. These ICC's indicate an adequate to good reliability of the RTF for all stimuli (Cicchetti & Sparrow, 1981).

To rule out decreased task engagement or general fatigue, reaction time values to the cartoon stimulus within subjects were compared. For both the control as the risk group, we calculated the RTF value of the first half of the sequence and of the second half of the sequence. A paired-samples T-test was performed to identify if RTF values of the second half of the sequence significantly ($p<0.05$) differed from RTF values of the first half of the sequence within one subject. The statistical analyses were performed in SPSS-17 (SPSS, Chicago, US).

Results

Informed consent was received for 134 (44%) of the 302 approached children. At the time of measurement, four children were unable to attend and three children had a visual acuity <0.1, resulting in 127 included children (53 females and 74 males, 7.73 (3.69) years, mean (SD)). In 29 children visual acuity measurement failed and their acuity was obtained from medical records. Of all 127 children, 30 wore glasses during the measurements, 11 had an abnormal head posture, 14 had visual field loss, 44 had strabismus, and 11 had nystagmus. In the children aged ≤4 years (n=39), 22 had a developmental and/or intellectual delay, eight had borderline, four had mild, two had moderate, and three had severe ID. In the group of children aged >4 years (n=88), one had borderline, 39 had mild, 32 had moderate, 12 had severe, and four had profound ID.

In the control group, we measured in 99% of the children reflexive orienting responses to the cartoon stimulus to determine an RTF value; in the risk group this percentage was 95% (n=120). In seven out of the 127 children in the risk group, no reaction times to the cartoon stimulus were available, or the values were excluded for further analysis based on the criteria as mentioned in the Methods section. Figure 5.4, top panel, shows the RTF values to the cartoon stimulus against the age of the children. The grey area illustrates the reference area of the controls. Of the 120 children, 86 (72%) had an RTF value above the reference area and were labeled with a delayed reaction time. Analyses of the different age groups showed delayed reaction times in 62% of the children aged ≤4 years and in 76% of the children aged >4 years (see also table 5.1). Figure 5.4, middle panel, shows the RTF values to the coherent form stimulus against age and the corresponding reference area. Note that the scaling of the y-axes is different in each panel. In the control group, we measured in 96% reflexive orienting responses; in the risk group this percentage was 75% (95 children). Overall, 47% had a delayed reaction time to the coherent form stimulus. In the group aged ≤4 years, this percentage was 31% compared to 54% of the children aged >4 years (table 5.1). During the presentation of the coherent motion stimulus in the control group, we were able to determine an RTF value in 88% of the children. For the risk

group this percentage was 50%, because in 64 of the 127 children we measured one or more reflexive orienting responses. From the other 50% of the children we did not have gaze data to calculate the reaction time to fixation. Of the 64 children with an RTF value, 38% had a delayed reaction time (figure 5.4, bottom panel). Again, the percentage was not evenly distributed across both age groups: 15% ≤4 years versus 43% >4 years (table 5.1). The reference area of the motion stimulus, illustrated in figure 5.2, bottom panel, showed the largest variability of RTF values compared to the other stimuli, and particularly in the youngest age group.

Mean RTF values of all stimuli per age group are summarized in table 5.2. In 122 children we calculated at least one RTF value for a stimulus type and in 101 children a minimum of two RTF values. In 56 of the 127 children, we calculated an RTF value for all three stimuli. Within this group, nine children had an RTF value within the normal range for all stimuli, 24 children scored a delayed reaction time to just one stimulus, 14 children to two stimuli, and nine children to all three stimuli.

The method aimed at measurement of the reflexive eye movement to a newly presented visual stimulus on the eye tracker's monitor. As stated, we were not able to measure this orienting response in 50% of the children during the presentation of the coherent motion stimulus. In 81% of these cases, gaze tracking failed due to lack of attention at the onset of a stimulus presentation. In 13%, the children showed pursuit like eye movements and in 6% the children did not make an eye movement to the target area at all. Other causes that might have led to failure of gaze tracking were wearing glasses, abnormal head posture, visual field loss, strabismus, or nystagmus. Wearing glasses and strabismus were most common in the risk group. On average, children with glasses had 2.2 times more often loss of gaze data compared to children without glasses. For children with strabismus this factor was 1.7.

The paired-samples T-test showed no significant difference between RTF values measured in the first half of the sequence compared to RTF values measured in the second half of the sequence for both the control group (n=190; p=0,166) as the risk group (n=120; p=0,469).

Table 5.1 - *An overview of the percentages of children in the risk group with delayed reaction times (delayed RTF), if an RTF value was available. The results show differences in percentage per age group and per stimulus.*

group	**n**	**% delayed RTF***		
		Cartoon stimulus	**Form stimulus**	**Motion stimulus**
≤4 years	39	21/34 (62%)	8/26 (31%)	2/13 (15%)
>4 years	88	65/86 (76%)	37/69 (54%)	22/51 (43%)

**the number of children with delayed RTF, divided by the number of children with available RTF values.*

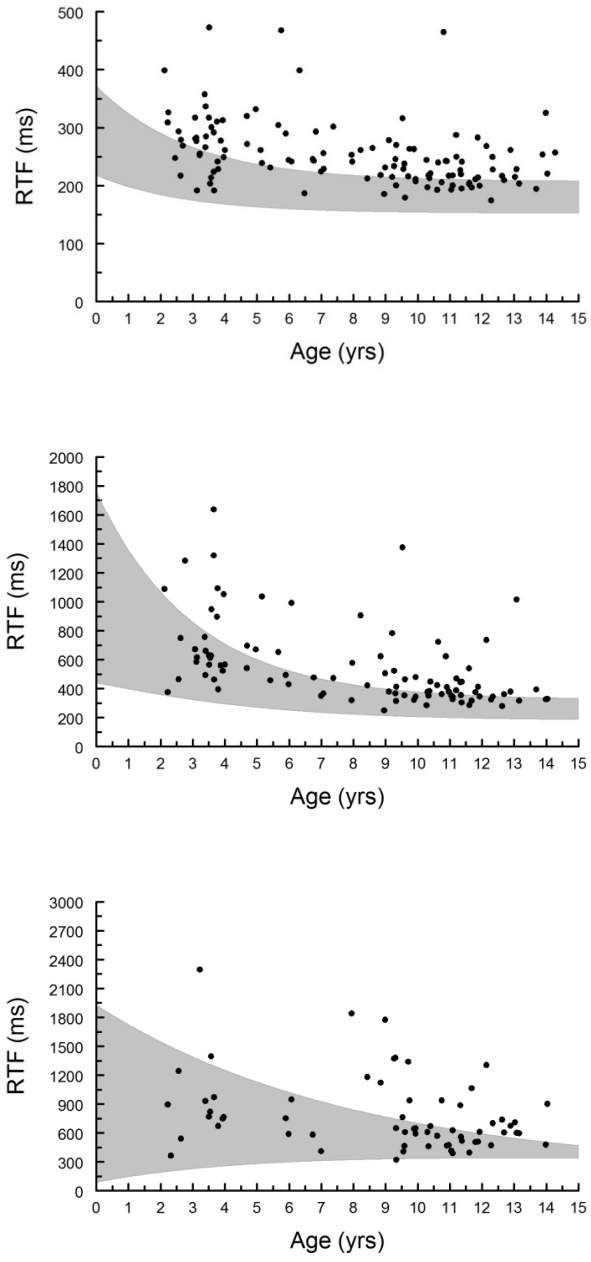

Figure 5.4 - *The RTF values of the children in the risk group are presented for the cartoon (top panel), form (middle panel), and motion (bottom panel) stimulus, together with the corresponding reference areas (gray areas). An RTF value above the upper border of the reference area was classified as a delayed reaction time and suggested difficulties in processing the visual stimulus.*

Table 5.2 - *An overview of the reaction times to fixation of three types of stimuli presented in the control and risk group. This table shows the mean RTF values per age group. For the risk group, children are divided in a group with RTF values within the reference area and a group with RTF values above the reference area (delayed RTF).*

group			**mean RTF (SD)**		
			Cartoon stimulus	**Form stimulus**	**Motion stimulus**
control	≤4 years		232ms (32)	663ms (207)	828ms (329)
	>4 years		189ms (19)	338ms (89)	580ms (169)
risk	≤4 years	RTF within reference area	227ms (23)	574ms (107)	794ms (230)
	>4 years		200ms (12)	355ms (64)	544ms (128)
	≤4 years	RTF above reference area	304ms (33)	1165ms (240)	1846ms (636)
	>4 years		247ms (29)	577ms (235)	1003ms (373)

Discussion

To our best knowledge, this is the first study that provides quantitative data on visual orienting responses using a remote eye tracking method in children with developmental and/or ID. The presence of delayed reaction times to fixation (RTF), indicating delayed orienting responses to visual stimuli, was highest in the group of children >4 years (4-14). Our results show that in a majority of the children with ID the RTF is longer compared with children with normal intelligence. Of the subgroup in which RTF values were obtained for all three types of stimuli allowing cross stimulus comparison, 38 out of 56 children had delayed reaction times to one or two of the stimuli and nine children to all three stimuli. Sandfeld Nielsen et al. described that abnormal visual acuity is related to a low IQ, thus children with ID have an increased risk for primary visual dysfunctions (Sandfeld Nielsen et al., 2007). The percentages of delayed RTF values in the risk group >4 years of the current study suggest that children with ID also have an increased risk for higher visual processing dysfunctions possibly in combination with ocular motor problems.

The eye tracking method made it possible to measure reflexive visual orienting responses in children with developmental and/or ID. As stated, visual orienting responses reflect visual processing including ocular motor control. Often the onset of an eye movement, the so-called saccadic reaction time (SRT), is used as a measure for visual processing time. In a previous study, we compared RTF values to cartoons with their corresponding SRT values in a subgroup of the present control group (Pel et al., 2010). SRT was derived from the moment that eye velocity of the saccade towards the target area where a cartoon was presented exceeded 50°/s. The difference between RTF and SRT was on average 60 ms (15 ms SD) and was regarded as an average measure for the duration of eye movements. Within our risk group, a similar approach resulted in

an average difference of 50 ms (20 ms SD) between the onset of the eye movement and landing of the eyes in the target area. This indicates that eye movement control was comparable between the risk group and the control group.

The success rate in measuring visual orienting responses depended on the type of stimulus and ranged between 50-94%. The three different visual stimuli, cartoon, coherent form, and coherent motion, were selected to test distinct visual processing aspects. As expected, each stimulus yielded different RTF values. The cartoon stimulus, however, resulted in the highest percentage of children with a delayed reaction time to the target area. This result seems paradoxical, because the cartoons consisted of oscillating, high contrast and colorful images and therefore draw visual attention faster than the more abstract black and white form and motion stimuli. A first explanation might be that this delay in orienting responses is caused by ocular motor dysfunction delaying eye movements to the cartoons. In an earlier study, we showed that, for example, congenital nystagmus in children with typical development significantly influences RTF values most likely due to fixation instabilities (Pel et al., 2011). However, this can only partly explain the delayed responses in our risk group, since only a minority of the children had to some degree a type of ocular motor problem, e.g. nystagmus or strabismus. Visual attention theories may provide an alternative explanation. These theories state that the brain constructs an internal saliency map based on features such as color, form, and movement (Koch & Ullman, 1985; Treue, 2003). The cartoon stimulus has a high foreground-background contrast ratio, it has colors, and it has motion features, as it moves with modest speed up and down. This would, according to the theory, yield a very high saliency, provided that these different visual aspects can be combined in a single winner-takes-all map. A possibility is that the generation of this final stage map is impaired in children with developmental and/or ID and would explain why the risk group in our study has more delayed reaction times to the cartoon compared to coherent form and coherent motion.

One would expect to find higher percentages in delayed responses to coherent form and motion as well. However, given the longer reaction times to coherent form and coherent motion in comparison to those to cartoon, it might be that in general children with or without ID need longer processing time of forming a salience map of these types of stimuli. In addition, in a recent paper on gaze allocation in complex picture viewing, it was stated that salience based schemes may be poor at accounting for many aspects during natural task performance (Tatler et al., 2011). Although our method aims at 'catching' the first reflexive orienting response (bottom-up processing) of much less complex visual stimuli, we acknowledge the possible influence of individual internal strategies (top-down processing). The results in our control group showed small variations in RTF values between children per age group for cartoon and coherent form. This suggests that for these two stimuli, guiding of eye movements is more bottom-up (salience driven)

than top-down. For the motion stimulus, we found much more variation in RTF values between children, which might be the result of more top-down influences. To improve validity of the reference areas, the power of the control group may be increased by inclusion of more children in future studies.

We found differences in proportion of delayed reaction times between preschool children aged ≤4 years and children aged >4 years, who attended special education. For all stimuli, the children >4 years showed a higher percentage of delayed reaction time compared to preschool children. In the group of children >4 years, all children had borderline to profound ID. However, a confounder may be that in the preschool group, also children were present with a developmental disorder but with normal intelligence. Children with an IQ in the normal range are expected to have a lower risk for visual impairment. In addition, the reference areas showed larger variations in RTF values for children ≤4 years than for children >4 years. At this stage, we do not know if this might explain why the majority of children ≤4 years had RTF values within the reference area. Further studies are needed, e.g. a longitudinal research in preschool children, to inform us about the development of visual orienting responses over time in combination with intellectual and motor development.

A limitation of the method was that in a number of children gaze data were not available to calculate the reaction time of the reflexive orienting response. In most cases, children were simply not looking at the eye tracker's monitor at the onset of presentation of visual stimuli and thus gaze data were not measured. This is most probably the result of short visual attention spans in a profound number of children with ID and to a much less extent the result of failure in gaze tracking. Another explanation could be a difference in task engagement or general fatigue within groups. However, when we compared reaction times within subjects to the cartoon stimulus, we found that these values do not alter much over time during the sequence. This means that the reaction times measured in the first half of the sequence are similar to those measured in the second half of the sequence within both groups. Insufficient eye tracking could have been the result of gaze signal obstruction due to e.g. a pair of glasses or misalignment of the eyes. We quantified, that wearing glasses resulted in about 2.2 times and strabismus in about 1.7 times more often loss of gaze data. Finally, a small portion of children made no eye movements and just stared at one point of the monitor, or they made pursuit like eye movements. This occurred especially during the presentation of the coherent motion stimulus.

Although the objective of our study was not to relate visual functioning to cognitive functioning, another way to present our results would be to plot RTF values as a function of developmental age instead of chronological age. Due to the levels of ID, the developmental age would be lower in the risk group. This would shift RTF values to the left in figure 5.4. Nevertheless, level of ID may be a risk factor for delayed reaction times, indicating a risk for

higher visual processing dysfunctions. We found that in the subgroup of 56 children, the majority of the children had a delayed reaction time to one or two out of three stimuli. This suggests that a variety of visual dysfunctions may exist within children with developmental and/or ID. In future studies, different experimental paradigms need to be investigated to test specific processing functions at different developmental stages. In addition, an attempt could be made to identify risk factors for impaired visual orienting responses, by correlating visual functioning to the medical history of the participants.

Our results suggest that a majority of the children with ID have impaired visual orienting responses which may relate to an increased risk of higher visual processing dysfunctions, possibly in combination with ocular motor disorders. With the eye tracking method, children with developmental and/or ID can already be screened for impaired visual orienting responses at a young age. The outcome provides an indication for individual support at an early stage during development. In time, the children with an increased risk should be referred to visual disability and rehabilitation centers for further assessment of higher visual processing dysfunctions.

Acknowledgements

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6.

Factors related to impaired visual orienting behavior in children with intellectual disabilities

Adapted from:

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Research in Developmental Disabilities; 2012 (33) 1670-1676

Abstract

Background

It is generally assumed that children with intellectual disabilities (ID) have an increased risk of impaired visual information processing due to brain damage or brain development disorder. So far little evidence has been presented to support this assumption. Abnormal visual orienting behavior is a sensitive tool to evaluate impaired visual information processing. Therefore, the main objective of this study was to investigate possible correlations between the children's characteristics (age, gender, level of ID, mobility, gestational age, cerebral palsy, Down syndrome, visual acuity, strabismus, nystagmus, and epilepsy), and abnormal visual orienting behavior.

Method

We quantified data on visual orienting behavior, in terms of visual processing time and ocular motor fixations, in 88 children with ID aged 4–14 years. These visual parameters were combined with data collected from the children's medical records (predictors) and were put in a Pearson bivariate correlation analysis. A predictor was included for multiple regression analysis if the Pearson's correlation coefficient had a level of significance of $p<0.05$.

Results

As shown by multiple regression analysis, age, level of ID, and Down syndrome significantly affected visual processing time. Mobility, strabismus, and nystagmus significantly affected fixation quality.

Conclusion

Using a systematic approach, we confirmed the hypothesis that children with ID have an increased risk of impaired visual information processing which is related to a low IQ.

Introduction

Children with brain damage or brain development disorders may experience problems in processing visual information. The so-called higher visual functions, such as form recognition, spatial orientation, visual memory, and motion detection, can be affected depending on type and location of brain pathology. Impairment of higher visual functions may have a severe effect on daily functioning and school performance. Studies focusing on visual dysfunctions caused by brain damage or a brain development disorder often use the medical term Cerebral Visual Impairment (CVI) (Dutton & Jacobson, 2001). It is still common that ophthalmologists define CVI as any visual problem that cannot be explained by ocular disease (Fazzi et al., 2009; Khetpal & Donahue, 2007). However, without neuropsychological assessment that specifies the types of visual processing dysfunctions, the diagnosis CVI does not provide a good starting point for understanding the child's visual problems, rehabilitation, and prognosis (Boot et al., 2010).

A group of children with a possible high risk of CVI are those with intellectual disabilities (ID). Recently, we found that a substantial part of the children with ID have delayed reaction times to fixating visual stimuli and therefore may have an increased risk of higher visual processing dysfunctions (Boot et al., 2012b). Other studies about this group of children have shown an increased prevalence of low visual acuity (≤6/18), visual field defects, refractive error, strabismus, and other ophthalmic disorders (Sandfeld Nielsen et al., 2008; Sandfeld Nielsen et al., 2007). The strong correlation with more severe ID, cerebral palsy, and epilepsy suggests that there is also an increased prevalence of higher visual processing dysfunctions. Higher visual (dys)functions have not been extensively studied in this group due to lack of adequate tests. Current neuropsychological diagnostic tests require a developmental level of at least 3–4 years. These tests, such as the visual perceptual battery L94, require motor and/or verbal responses to assess the child's perception level (Stiers et al., 2001). Assessments of higher visual functions in children with ID are mainly based on observation. An observer presents different types of stimuli and assesses which types of materials the child prefers to watch, if the child can distinguish between colors or shapes, and how he or she reacts on motion. Eye movements are judged by the observer to determine if a child has seen the stimulus or not. The disadvantage of observer-based assessments is that they depend on the experience of the professional and do not give a quantitative outcome on reaction times or accuracy of fixation. As a result, still little is known about the prevalence and specific types of higher visual dysfunctions in children with ID.

At our department, we developed an objective method based on automatic detection of ocular motor responses. Eye movements are measured with a remote eye tracker (Pel et al., 2010). This method allows us to quantify visual orienting behavior in very young children (from four months old) and in children with developmental and/or intellectual disabilities (Boot et al.,

2012b; Pel et al., 2011). The technique is based on the behavioral discrimination task preferential looking (Fantz, 1965). Preferential looking, which is also used in Teller or Cardiff cards (Sturm et al., 2011; Teller, 1979), is based on the principle that visual stimuli induce reflexive eye movements towards a stimulus. With the quantification of visual orienting responses, one tests the integrity of the complete visual pathways (peripheral and central) and the ocular motor system (Noton & Stark, 1971a; Noton & Stark, 1971b; Yarbus, 1967). Impaired visual orienting responses may relate to an increased risk of higher visual processing dysfunctions, possibly in combination with ocular motor disorders. We present a variety of visual stimuli on an eye tracker monitor while gaze is recorded. No specific verbal instructions prior to the test or active cooperation are needed. Children can be tested in familiar surroundings and the duration of the measurement is relatively short (~15 min). Two parameters are calculated from visual orienting responses, i.e. the reaction time to fixating a target area and the gaze fixation quality (Pel et al., 2010). The reaction time to fixation (RTF) reflects processing of visual information and the ocular motor response. The gaze fixation area (GFA) relates to ocular motor pathology that may influence visual input. We studied a large cohort of typically developing children and found decreasing RTF with increasing age. The different reaction times for different visual stimuli suggest that maturation of processing high contrast cartoons, coherent form, and coherent motion follow different timelines (Boot et al., 2012a; Pel et al., 2011).

In the present study, we combined our previous data on visual orienting behavior in children with ID (RTF and GFA data), with data collected from medical records of the same group of children. The main objective of this study was to provide first insights into correlations between the children's characteristics (age, gender, level of ID, mobility, gestational age, cerebral palsy, Down syndrome, visual acuity, strabismus, nystagmus, and epilepsy), and impaired visual orienting behavior. This can be seen as a first step to identify risk factors of visual processing dysfunctions in children with ID. If risk factors are known, these children could be screened at an early age. Their visual dysfunctions can be specified and correct daily support and rehabilitation can be given. With an individual approach we want to improve their psychosocial development, daily functioning, and school achievement.

Methods

Participants

For the current study, the parents of 207 children with ID aged 4–14 years in the Rotterdam and Leiden regions of The Netherlands were informed about the study by letter. Children were approached through two types of schools for special education. The first type of school was

designed for children with mainly an intellectual disability in an IQ range of 20–70. The second type of school educated children with an intellectual disability (IQ < 70) in combination with a motor disability. After informed consent, information on age, gender, level of ID, mobility, gestational age, etiology of the disabilities, visual status, and antiepileptic drug use was gathered. this information was retrieved from medical records available at the schools and from self-made questionnaires completed by the parents of the participants. Level of ID was categorized into borderline, mild, moderate, severe, and profound, according to ICD-10 (International Classification of Disease). Mobility was divided into three categories: able to walk independently (GMFCS 1 and 2), able to walk with support (e.g., walker or walking frame) (GMFCS 3), and wheelchair-bound (GMFCS 4 and 5). As part of the measurement, all children were screened for abnormal visual acuity using visual acuity cards (Teller or Lea Hyvärinen single symbols cards). If screening failed, we used visual acuity found in medical records that was assessed at an earlier stage by a physician or optometrist. Children with an acuity <0.1 (10%; LogMAR 1.00; Snellen 20/200) and children with ocular motor apraxia were excluded from this study.

Visual orienting responses

All children were shown a cartoon, a coherent form, and a coherent motion expansion stimulus, presented on a remote infrared eye tracking monitor (Tobii T60XL, Tobii Corporation, Sweden). A full description of the stimuli has been reported elsewhere (Boot et al., 2012b). All stimuli contained a specific area in one of the quadrants of the monitor, defined as the target area. The target area of the cartoon stimulus was a colored cartoon from a collection by Dick Bruna (creator of Miffy the rabbit), which was shown 24 times during one sequence. The target area of the form stimulus consisted of coherently orientated short white lines that form a curved pattern. The motion stimulus consisted of an expansion of white dots, which originated in the target area and moved to the borders of the monitor. The form and motion stimulus were repeated four times during one sequence. All measurements were stored on the hard disk and manually analyzed off-line using self-written Matlab programs (Mathworks Inc., Natick, MA, USA).

Reaction time was based on eye movement responses. For each stimulus presentation, reaction time was defined as the time when the stimulus was shown on the monitor (t=0 s) until gaze was within the target area. A cumulative plot was constructed of the available reaction time values (at least one) per stimulus. An exponential curve was fitted to this cumulative plot to quantify the reaction time as the minimum reaction time (t_{min}) plus 1/3 of the time constant τ of the exponential curve. This value was denoted as the reaction time to fixation (RTF). The focus of gaze analysis was to assess reflexive orienting eye movements to the target area as a best estimate of visual processing time.

Fixation quality was calculated for the cartoon stimulus only and could be determined using principle component analysis (Oliveira et al., 1996). Gaze fixation area (GFA) was expressed as an average diameter in degrees if the target area was detected. During presentation, each cartoon stimulus had an oscillatory movement, but with modest speed and amplitude. No corrections were made in calculating the average GFA values.

Statistical analysis

First, a Pearson bivariate correlation analysis was performed between the participants' characteristics (predictors) and the four visual orienting parameters RTF cartoon, GFA cartoon, RTF form, and RTF motion (dependent variables). If the Pearson's correlation coefficient had a significant value of $p<0.05$, the predictor was included for multiple regression analysis. Second, linear multiple regression was performed to determine outliers. Cases with an absolute standardized residual of >3 were excluded for further analysis. Third, linear multiple regression analysis was performed again to investigate to what extent personal characteristics influence the quality of visual orienting behavior. To investigate multicollinearity, values of Tolerance had to be >0.10 and the Variance Inflation Factor (VIF) <10.0. In addition, Pearson correlation coefficients were used to check for high correlations between predictors. The explaining value of the regression model was calculated with R^2, as the percentage of variance explained by the model. The standardized coefficients (β's) were presented to compare the magnitude of the influence of the different predictors and were checked for significance ($p<0.05$). For all regression models cases were excluded pairwise to ensure that all available data was used for analysis. The statistical analyses were performed in SPSS-17 (SPSS, Chicago, US).

Study design

This study is part of a large cross-sectional study to measure visual orienting behavior in children 0–14 years, which has been executed since 2007 by the Erasmus Medical Center and Royal Visio (a Dutch organization for people who are blind or visually disabled). Children with normal intellectual, motor, and visual development were included as the control group, whereas the risk group consisted of children who are at risk for brain damage or brain development disorders. This group includes children with developmental and/or intellectual disabilities, children with motor disabilities and children diagnosed with nystagmus. The experimental procedures were approved by the Medical Ethical Committee of Erasmus University Medical Center, Rotterdam, The Netherlands (METC-2006-055). The study adhered to the Declaration of Helsinki for research involving human subjects.

Results

Informed consent was received for 92 children (44%). At the time of measurement, three children were unable to attend and one child had a visual acuity <0.1, resulting in 88 included children (32 females and 56 males, 9.73 (2.51) years, mean (SD)). Participants' characteristics are presented in table 6.1. Etiologies of their intellectual disability were congenital birth defect (n=1), metabolic disorder (n=1), infection (n=6), hypoxia (n=17), genetic disorder (n=28), and unknown (n=35).

Data of the 88 children were used for correlation and regression analysis. Data of the motion stimulus showed no significant correlations and the number of children with successful measurements was limited (n=51). Gaze tracking failed if: (1) a child showed a lack of attention at the onset of a stimulus presentation, (2) a child showed pursuit like eye movements which could not be used to calculate the RTF or GFA, or (3) a child did not make an eye movement to the target area at all. Other causes that might have led to failure of gaze tracking were wearing glasses, abnormal head posture, visual field loss, strabismus, or nystagmus. As a result, data of the motion stimulus were not included for multiple regression analysis. For the cartoon and form stimulus, predictors that showed a significant bivariate correlation (Pearson; $p<0.05$) with dependent variables were included in the regression model, see table 6.2. Each dependent variable had one or two outliers (standard residual >3.0) which were excluded for further analysis. Nystagmus showed a high bivariate correlation (Pearson >0.45–0.50) with mobility and strabismus, and was therefore separately entered into the regression model. Thus, the variables were first entered all together, subsequently the model was repeated without nystagmus, and next without strabismus and mobility. The results are shown in table 6.2. For all variables in each model, the Tolerance was >0.10 and the Variance Inflation Factor (VIF) was <10.0, which excluded multicollinearity.

Age significantly affected the outcome of the RTF value when the cartoon or form stimulus was presented: the older a child gets, the faster the reaction time. For the cartoon stimulus alone, several predictors influenced the quality of visual orienting behavior: (1) a lower IQ was related to a slower reaction time and poorer fixation quality, (2) a more severe motor disability was related to poorer fixation quality, as were strabismus and nystagmus, and (3) Down syndrome was related to an impaired reaction time. Furthermore, GFA and RTF values, obtained during the presentation of the cartoon stimulus, had a significant correlation with each other (Pearson coefficient of 0.250; $p<0.05$).

Table 6.1 - *Characteristics of the participants.*

	Participants	
	n	**% of category**
Total	**88**	**100.0**
Gender		
Male	56	63.6
Female	32	36.4
Level of ID		
Borderline	1	1.1
Mild	39	44.3
Moderate	32	36.4
Severe	12	13.6
Profound	4	4.6
Mobility		
Walks independently	70	79.5
Walks with support	2	2.3
Wheelchair	16	18.2
Gestational age		
<32 weeks	1	1.2
≥32weeks	81	92.0
unknown	6	6.8
Cerebral Palsy		
+	15	17.0
-	73	83.0
Down syndrome		
+	11	12.5
-	77	87.5
Visual acuity		
0.1-0.33	12	13.6
>0.33	66	75.0
unknown	10	11.4
Strabismus		
+	26	29.6
-	61	69.3
unknown	1	1.1
Nystagmus		
+	8	9.1
-	79	89.8
unknown	1	1.1
Antiepileptics		
+	22	25.0
-	66	75.0

+ present; - not present.

Table 6.2 - *Bivariate correlations and regression models of reaction time (RTF) and fixation quality (GFA). Gender (male=1, female=0); Level of ID (borderline=0, mild=1, moderate=3, severe=4, profound=5); Down syndrome (not present=0, present=1); Mobility (no support=0, support=1, wheelchair=2); Strabismus (not present=0, present=1); Nystagmus (not present=0, present=1); Antiepileptics (not present=0, present=1).*

PAIRWISE	n	Bivariate correlation	Multiple regression		
			ANOVA R^2	Sign.	Coefficients β
RTF cartoon	86		0.242	p=0.001	
Age		- 0.340**			- 0.292*
Gender		- 0.141			
Level of ID		0.216*			0.272*
Mobility		0.126			
Prematurity (<32 weeks)		- 0.039			
Cerebral Palsy		0.055			
Down syndrome		0.240*			0.254*
Visual acuity		- 0.275*			0.005
Strabismus		0.136			
Nystagmus		0.255*			- 0.005
Antiepileptics		0.027			
GFA cartoon	87		0.396	p<0.001	
Age		- 0.247*			0.057
Gender		- 0.154			
Level of ID		0.465**			0.235*
Mobility		0.477**			0.259***
Prematurity (<32 weeks)		- 0.073			
Cerebral Palsy		0.185			
Down syndrome		- 0.053			
Visual acuity		- 0.439**			- 0.190
Strabismus		0.400**			0.217***
Nystagmus		0.515**			0.295***
Antiepileptics		0.077			
RTF form	69		0.408	p<0.001	
Age		- 0.345**			- 0.300*
Gender		- 0.288*			- 0.169
Level of ID		0.374**			0.179
Mobility		0.334**			0.012
Prematurity (<32 weeks)		- 0.082			
Cerebral Palsy		0.064			
Down syndrome		0.173			
Visual acuity		- 0.320*			- 0.219
Strabismus		0.273*			0.062
Nystagmus		0.151			
Antiepileptics		0.238*			0.143
RTF motion	51		Non applicable		
Age		- 0.234			
Gender		- 0.123			
Level of ID		0.190			
Mobility		0.009			
Prematurity (<32 weeks)		- 0.015			
Cerebral Palsy		- 0.148			
Down syndrome		- 0.062			
Visual acuity		- 0.242			
Strabismus		0.075			
Nystagmus		0.157			
Antiepileptics		0.075			

** p<0.05; ** p<0.01; ***p<0.05: high correlation (>0.45) between Nystagmus and Mobility, and Nystagmus and Strabismus. Nystagmus is separately put in regression model.*

Discussion

In a group of 88 children with ID aged 4–14 years, correlations between the children's characteristics (age, gender, level of ID, mobility, gestational age, cerebral palsy, Down syndrome, visual acuity, strabismus, nystagmus, and epilepsy), and their visual orienting responses to cartoon, form coherence, and motion coherence were studied. Age, level of ID, and Down syndrome significantly influenced the reaction time to the cartoon stimulus. This result suggests that processing of such a stimulus takes more time for low IQ children and children diagnosed with Down syndrome. Motor impairment, nystagmus, and strabismus were significantly related with an enlarged gaze fixation area during the presentation of the cartoon stimulus. Although this shows that peripheral ocular motor pathology influences fixation quality, it does not necessarily influence the processing time. In general, our results indicate that risk factors of visual processing dysfunctions may exist within children with ID. A longitudinal research setup is needed to investigate the specific risk factors in this group of children using the remote eye tracker method.

The correlation between age and reaction time to fixation for both cartoon and form coherence confirms former research on maturation of visual processing functions during childhood in typically developing children (Mercuri et al., 2007). Visual functioning in children with developmental disorders has been studied previously, however with a focus on ophthalmological disorders. Here it was shown that abnormal visual acuity was related to low IQ (Sandfeld Nielsen et al., 2008; Sandfeld Nielsen et al., 2007). In our study, bivariate analysis showed significant correlations between visual acuity and orienting responses to cartoon and form. However, in the multiple regression analysis these correlations disappeared against other factors. One would expect to find a correlation between low visual acuity and delayed fixation quality, and between low visual acuity and increased visual processing time. An explanation might be that we obtained suboptimal visual acuity values. We consequently performed the visual acuity test after the remote eye tracking task. It could be that reduced attention has led to unrepresentative values of visual acuity. The other explanation might be that if visual acuity does indeed not influence these visual outcomes, our method can be used to assess higher visual functions in children with any visual acuity value >0.1. We suggest that in future studies using the same method, visual acuity measurements are done at a different moment in time.

Despite the method's favorable applicability in practice, we report a number of limitations of this study as well. We emphasize that this is a first explorative study with a low number of participants. In future studies the power of the risk group may be increased to improve validity of the multiple regression models. Another consequence of the relatively low number of participants is that not enough data were obtained for visual orienting responses to the motion stimulus in order to find significant correlations. The explaining values of the models in the current study,

calculated with R^2, are between 0.242 and 0.408, which indicates that approximately 24–41% of visual orienting behavior is explained by the included predictors. Other factors that are of influence on visual orienting responses remain unknown with the current analysis. These factors might include attention deficits disorders and risk factors of brain damage, e.g. asphyxia. Specific syndromes, e.g. fragile-X syndrome and Williams syndrome which are associated with difficulties in visual spatial cognition, could be included in future studies (Grinter et al., 2010).

Overall, with this study a first approach was realized to identify factors of children with ID that are related to higher visual processing dysfunctions. The prevalence of higher visual processing dysfunctions may be more pronounced in this group of children than we are currently aware of. For that reason we would like to emphasize that more research into this field is needed. In view of the postnatal maturation of the visual system, it would be best to detect dysfunctions as early as possible during infancy. However, a diagnosis based on anatomical landmarks may be inefficient. In fact, several explanations confirm why it is not possible to assign a particular visual dysfunction to a single brain structure and dissociate visual processing areas. First, different visual pathways are strongly interconnected and multiple areas are involved during visual processing. Second, a possible overlap of lesions complicates a clear anatomical delineation. Third, a combination of peripheral and central damage is often seen in one patient and it has been shown that peripheral defects can also influence central visual information processing (Simonsz et al., 2009). In our view, a more promising approach is to assess the different types of higher visual dysfunctions in each child. If it is possible to detect which types of visual dysfunctions are present, one can adjust daily support and improve individual rehabilitation. Application of a remote eye tracker makes it possible to objectively assess visual orienting behavior to specifically chosen visual stimuli. If, in the future, it is known which group of children has an increased risk of specific visual dysfunctions, screening should have highest priority in this group of children. As a result, optimum individual support can be provided at an early stage of visual maturation.

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7.

General Discussion

General Discussion

Main findings and conclusions

The work presented in this thesis emerged from the need to advance the diagnosis of cerebral visual impairment (CVI) from a diagnosis per exclusion to an approach in which the diagnosis of CVI can be based on quantitative parameters. Children with intellectual disabilities have not only an increased risk of CVI due to brain damage or brain development disorders, but also an increased risk that CVI is not detected. In current clinical practice, a variety of neuropsychological test methods are used to diagnose higher visual dysfunctions in CVI. For example, the visual perceptual battery L94 (Stiers et al., 2001), the judgment of line orientation (JLO) test (Benton et al., 1983), the Birmingham Object Recognition Battery (BORB) (Riddoch & Humphreys, 1993), the Labyrinth (LA) test (Tewes et al., 2001), and the Woodcock-Johnson-Spatial Relations (WCJ-SR) test (Woodcock & Mather, 1989). A limitation of existing test methods is that they require a developmental level of four years and motor or verbal responses to complete the test. Because of these limitations, assessment in children with intellectual disabilities is mostly restricted to observations of eye movements. Observation of impaired visual orienting responses may indicate an increased risk of CVI. However, a child's additional neurological problems, such as involuntary movements of limbs, abnormal head posture, nystagmus, or strabismus, can interfere with the interpretation of their eye movements. The lack of adequate test methods is the main reason that diagnosis of CVI in children with intellectual disabilities is mainly based on exclusion criteria and can often be completely missed. As a result, the actual prevalence remains largely unknown.

The method we used in this thesis is a first approach to come to a more quantitative diagnosis of CVI based on the assumption that CVI results in a partial or complete functional impairment of cerebral visual information processing. The work presented in this thesis shows that the preferential looking approach in combination with objective recording of eye movements can effectively be used in normally developing children as well as in children with intellectual or motor disabilities. The main reason that we could apply this method in children aged 0-14 years with normal development and in children of the same age with developmental and/or intellectual disabilities is that the technique requires no verbal responses or active cooperation. A first general conclusion we can draw from our work is that remote eye tracking in combination with a preferential looking technique offers the opportunity to measure visual orienting behavior from a very young age, both in healthy children as in children with intellectual disabilities.

A second important result of our work is that the quality of visual processing functions can be quantified. We quantified visual orienting responses in terms of reaction time to fixation (RTF) and gaze fixation area (GFA). One of the main advantages to have quantitative outcome parameters in children with CVI is that they potentially allow to study links between functional and

anatomical damage, to make comparisons between groups, and to follow visual functioning over time.

In the section below we will discuss which conclusions can be drawn from previous research on CVI, what the main implications are from the studies described in this thesis, and which future studies are needed to advance our knowledge on CVI and its implications for rehabilitation practice.

In chapter 2 we present a review of current knowledge on possible correlations between etiologies, locations of brain damage, and higher visual dysfunctions in children diagnosed with CVI. The diagnosis of CVI, based on anatomical markers alone, included those children with visual impairment that could not be explained by ophthalmologic pathology. We found that current literature does not allow to draw a solid conclusion, neither on causes nor on effects of cerebral visual dysfunction. The lack of a correlation between structural damage and its effect on cerebral visual processing dysfunction raises the question if, in view of the variability in structural damage, the diagnosis of CVI may be based on anatomical markers alone. Instead we propose that the diagnosis of CVI should also be based on functional tests. Therefore we will use the term cerebral visual processing dysfunctions (CVPD) in the remainder of the discussion, as we believe that this term gives a better reflection of the underlying pathology. The outcome of the review described in chapter 2 reiterates the need to have more direct measures of a child's functional performance in cerebral visual processing. An individual description of the types of CVPD per child provides a good starting point for understanding the child's visual problems, for rehabilitation and to improve prognosis.

Chapter 3 underlines our conclusion that the preferential looking method based on remote eye tracking can provide objective data on CVPD. In this chapter we compared a group of children aged 2-14 years diagnosed with CVPD with a healthy control group. The (probable) diagnosis of CVPD was based on an abnormal visual acuity without ocular pathology, on neuropsychological assessments, and observations. In this study we showed that the CVPD group had a prolonged RTF compared to the controls. This does not yet prove that children with CVPD are generally slower in processing visual information, because children with CVPD may also have ocular motor problems, such as nystagmus. For this reason we also compared the group of children diagnosed with CVPD (with and without nystagmus) with a group of children having congenital nystagmus only. Children with CVPD had a significantly longer RTF compared to children with congenital nystagmus only. In addition, children diagnosed with CVPD in combination with nystagmus and children with congenital nystagmus only had a larger GFA compared to children with CVPD without nystagmus. GFA represents the gaze area that is used when focusing on a stimulus or an area of the stimulus, and is related to fixation quality. A larger GFA value signifies lower fixation quality

(and vice versa). This means that ocular motor problems do influence fixation quality but do not necessarily influence visual processing time. The main overall conclusion we can draw from this chapter is that parameter values collected with the remote eye tracking method are sensitive enough to distinguish between normal visual processing, impaired visual processing, and ocular motor disorders.

As a next step, we investigated in chapter 4 if different higher visual functions have different performance during development with age. To this end we compared coherent form with coherent motion processing in the healthy control group. Form and motion processing can serve as indicators of two distinct cortical visual networks, the ventral and dorsal stream respectively. In the control group we indeed found different developmental trajectories for the processing time of coherent form and coherent motion, and we concluded that coherent form processing reaches adult levels at an earlier age than coherent motion processing. The timelines were similar to the developmental trajectories found in published studies applying psychophysical threshold detection methods. It provides first validity to the use of reaction time to fixation, measured with the remote eye tracker, as an outcome parameter to study higher visual processing functions.

In chapter 5, we used the outcome of the control group for three different stimuli, i.e. cartoon, coherent form, and coherent motion, to define age-related reference values. Compared to these reference values we showed in chapter 5 that a majority of the children with intellectual disabilities had a prolonged RTF. This delayed visual processing time may relate to an increased risk of CVPD, possibly in combination with ocular motor disorders. Most children had prolonged visual processing time to one or two of the three analyzed visual stimuli, suggesting that a partial impairment of visual dysfunctions may exist within children with intellectual disabilities. For example, a child may have problems in detecting motion, but may perfectly recognize a circle.

In chapter 6 we studied correlations with individual characteristics and revealed that age, level of intellectual disability, and Down syndrome were related to a prolonged RTF. For the GFA we found that a decrease in fixation quality was related to a lower IQ, more severe motor disability, and ocular motor deficits nystagmus and strabismus. This shows that peripheral ocular motor pathology influences fixation quality, but does not necessarily influence processing time in this risk group.

An important visual parameter measured in this study was the RTF. The RTF represents the time of visual processing from the moment that the visual information is presented on the remote eye tracking monitor until an ocular motor response has been made. Perception, i.e. to understand what is seen and give verbal or motor responses, might not even be completed yet. One tests the integrity of the complete visual pathways and the ocular motor system, from retinal input to ocular motor output. Based on reference values of the control group, delayed RTF values were

determined in risk groups and may relate to an increased risk of CVPD for the presented stimulus. However, it remains unknown at which level of visual processing this delay originates. We do know that eye movement control was comparable between the control group and the risk group. The ocular motor input to make an eye movement was on average 60 ms (15 ms SD) in the control group and 50 ms (20 ms SD) in the risk group, as described in chapter 5.

Road map to general applicability

An important outcome of our study is that it generates the possibility to apply the remote eye tracking method in children who are difficult to assess with current test methods. The advantage of the method is that children of all ages, starting at approximately four months old, and all intellectual levels can, in principle, be assessed. No instructions, assignments, or verbal responses are necessary. Eye-hand related demands, e.g. pressing a button, are avoided and the method compensates for free head movements. The duration of the measurement is relatively short (15 minutes), the method is non-invasive, and has a low burden for children. Since the equipment is portable, the measurements can be performed at schools or at other familiar surroundings for the child. Still, a number of children were excluded for further analysis due to missing gaze data, which is related to the quality of the data and visual attention of the child.

Concerning the quality of gaze data, the eye tracker had problems of detecting the eyes in some children who wore glasses or had strabismus. Particularly in children who had strabismus, we had to solve the problem of calibrating two eyes. The eye tracker system calculates gaze positions based on the conjugate behavior of the two eyes. In our study we solved this problem by applying a post-hoc analysis written in Matlab. However, it would be an improvement if this could be solved in the hardware. Concerning visual attention, children showed a lack of task engagement at the onset of a stimulus presentation. As a result, gaze data had to be excluded more often than we expected at the beginning of this study. A future solution to this problem would be to modify stimuli presentations. Currently, stimuli are presented as an uninterruptable movie stream. An interactive set-up within the remote eye tracking method and analysis, which can be adjusted to the child's visual attention and behavior, may increase the amount of valid gaze data.

Another limitation of the new method relates to the stimulus type. Although we showed that a majority of young children and children with intellectual and/or motor disabilities were able to participate and complete the newly developed test, the stimulus type determined the success rate of the data analysis. In particularly for the motion stimulus, a majority of the children did not have enough gaze data to calculate the visual processing time. In the future, different types of motion stimuli should be analyzed to increase the method's applicability for testing coherent

motion processing. In addition, the power of the risk group has to be increased to validate the best applicable stimuli for testing different higher visual functions in this group of children.

To obtain optimal reference values, it is necessary to expand the number of controls. Because reference values are age-dependent, we used calendar age-related reference values of the control group to make a graphical reference area of visual processing time against age. The largest spread and variety of RTF values were found in children younger than four years of age, especially for the coherent motion stimulus. Since it would be best to detect visual dysfunctions as early in infancy as possible, the size of the control group in this youngest age range should be increased to improve the validity of the presented reference areas.

In this thesis, we analyzed developmental trajectories of visual processing time of three different visual modalities: cartoon, coherent form, and coherent motion. During one sequence, several other visual stimuli were assessed as well. These stimuli were designed to test ocular motor functions, such as saccades and smooth pursuit, and other visual functions such as color vision and contrast sensitivity. Ideally, for clinical application one should test and analyze as many visual modalities and functions as possible.

Suggestions for future research

The remote eye tracking method is currently further assessed in a larger population. An important aim is to validate the method, by comparing the eye tracker based outcomes with currently used standard neuropsychological test methods in a control group of children who are capable to perform both test methods correctly. We suggest that in future studies other types of visual stimuli should be presented and analyzed to determine which stimuli are applicable for valid assessment of different visual functions in young children and in children with intellectual disabilities. This study shows that a majority of the children with intellectual disabilities have an increased risk of CVPD. We identified some factors (age, level of ID, and Down syndrome) within this group of children that are related to an increased risk of CVPD. A longitudinal research set-up in a larger group of children with intellectual disabilities is needed to confirm our findings and to identify more possible risk factors, such as other genetic syndromes. Apart from children with intellectual disabilities, it would be important to study more homogenous subgroups, such as children who were born premature, children with hypoxic ischemic injury during birth, children diagnosed with periventricular leukomalacia, hydrocephalus, or meningitis. Studies with these types of risk groups will give more insights in the prevalence and risk factors of CVPD. Another important step towards understanding the causes of CVPD would be to combine the outcomes of the remote eye tracking method with brain imaging (e.g. DTI imaging) in order to relate anatomical structures with visual functioning.

The clinical value for children with intellectual disabilities

At this stage, we may conclude that the remote eye tracking method makes it possible to objectively assess visual orienting behavior in children with mild to profound intellectual disabilities, with and without motor or other neurological problems. The assessment of visual orienting behavior gives a first impression about visual processing time and ocular motor quality. The method reveals which visual information leads to activation of the ocular motor system, although the visual perception of the child remains unknown when verbal or motor responses are not assessed. Ideally, we would want to use the remote eye tracking method: (1) as a screening method before current neuropsychological test methods can be applied, (2) as an instrument to provide visual training, (3) to measure the effect of individual support and visual training, and (4) to relate visual orienting behavior to the following actions of the child and then determine which visual information is used in daily life. This could make professionals aware how to influence daily functioning, general development, and even school performance of the child.

General Conclusion

The results of this study should make us aware of the high risk of CVPD in children with developmental and/or intellectual disabilities. Our advice to clinical practice is that all children with intellectual disabilities should be screened at a young age for CVPD and, if needed, referred to a rehabilitation center for low vision. We showed that visual orienting behavior can be quantified in very young children and in children with intellectual and/or motor disabilities. Our approach may enable us to obtain quantitative outcomes by objective assessment of eye movements. This thesis reports first leads to use quantification of eye movements as a diagnostic measure for higher visual dysfunctions in children with intellectual disabilities. Although it does not assess visual perception, it can inform us about the visual processing abilities of children and their ocular motor control. If further development of the method's gaze tracking and analysis is completed, the remote eye tracker can be used as a screening method for CVPD. Hopefully in the future it can even be used as a diagnostic instrument for CVPD. Instead of labeling a child with the very broad diagnosis CVI by exclusion, it may be possible to diagnose specific types of higher visual processing dysfunctions with the eye tracking method in early childhood. A separate description of the different types of visual dysfunctions within one child could be useful and a good addition in clinical practice.

References

References

Abadi R.V., Whittle J.P. & Worfolk R. (1999) Oscillopsia and tolerance to retinal image movement in congenital nystagmus. *Investigative Ophthalmology and Visual Science* (40) 339-345.

Altman D.G. (1993) Construction of age-related reference centiles using absolute residuals. *Statistics in Medicine* (12) 917-924.

Aminoff M.J., Boller F. & Swaab D. F. (2008) Malformations of the nervous system. *Handbook of clinical neurology, 3rd series ed.* (87) 453-455.

Atkinson J. (1992) Early visual development of parvocellular and magnocellular pathways. *Eye* (6) 129-135.

Benton A.L., Hamsher K.D., Varney N.R. & Spreen O. (1983) Contributions to neuropsychological assessment: a clinical manual. *Oxford: Oxford University Press.*

Bhasin T. K., Brocksen S., Avchen R. N. & Van Naarden Braun K. (2006) Prevalence of four developmental disabilities among children aged 8 years--Metropolitan Atlanta Developmental Disabilities Surveillance Program, 1996 and 2000. *MMWR Surveillance Summaries* (55) 1-9.

Bland J.M. & Altman D.G. (1999) Measuring agreement in method comparison studies. *Statistical Methods in Medical Research* (8) 135–160.

Boonstra N., Limburg H., Tijmes N., van Genderen M., Schuil J. & van Nispen R. (2011) Changes in causes of low vision between 1988 and 2009 in a Dutch population of children. *Acta Opthalmologica Scandinavica* doi: 10.1111/j.1755-3768.2011.02205.x

Boot F.H., Pel J.J.M., Evenhuis, H.M. & van der Steen J. (2012a) Quantification of visual orienting responses to coherent form and motion in typically developing children aged 0–12 years. *Investigative Ophthalmology and Visual Science* (53) 2708-2714*.*

Boot F.H., Pel J.J.M., Vermaak M.P., van der Steen J., Evenhuis H.M. (2012b) Delayed visual orienting responses in children with developmental and/or intellectual disabilities. *Revision submitted.*

Boot F.H., Pel J.J.M., van der Steen J. &Evenhuis H.M. (2010) Cerebral Visual Impairment: which perceptive visual dysfunctions can be expected in children with brain damage? A systematic review. *Research in Developmental Disabilities* (31) 1149-1159.

Braga L.W., Souza L.N., Najjar Y.J. & Dellatolas G.(2007) Magnetic resonance imaging (MRI) findings and neuropsychological sequelae in children after severe traumatic brain injury: the role of cerebellar lesion. *Journal of Child Neurology* (22) 1084-1089.

Canfield R.L., Smith E.G., Brezsnyak M.P., Snow K.L. (1997) Information processing through the first year of life: a longitudinal study using the visual expectation paradigm. Monographs of the Society for Research in Child Development (62) 145.

Cans C., Guillem P., Fauconnier J., Rambaud P. & Jouk P. S. (2003) Disabilities and trends over time in a French county, 1980-91.*Archives of Disease in Childhood* (88) 114-117.

Cicchetti D.V. & Sparrow S.A. (1981) Developing criteria for establishing interrater reliability of specific items: applications to assessment of adaptive behavior. *American Journalof Mental Deficiency* (86) 127-137.

Coenen-van Vroonhoven E.J.C.,LantauV.K., van Eerdenburg-KeuningI.A.&van Velzen-MolH.W.M.(2010) Opsporing visuele stoornissen 0-19 jaar, Eerste herziening.*JGZ-richtlijn,*Rapport 295001014.

Corballis M.C. & Finlay D.C. (2000) Interhemispheric visual integration in three cases of familial callosal agenesis. *Neuropsychology* (14) 60-70.

Corbetta M., Patel G., Shulman G.L. (2008) The reorienting system of the human brain: from environment to theory of mind. *Neuron* (58) 306-324.

Corbetta M. & Shulman G.L. (2002) Control of goal-directed and stimulus-driven attention in the brain. Nature Reviews Neuroscience (3) 201-215.

Deguchi K. & Miller G. (2009) Periventricular Leukomalacia. *Up to Date* http://www.uptodate.com/contents/periventricular-leukomalacia

Dutton G.N. (2003) Cognitive vision, its disorders and differential diagnosis in adults and children: knowing where and what things are. *Eye* (17) 289-304.

Dutton G.N. & Jacobson L.K. (2001) Cerebral visual impairment in children. *Seminars Neonatology* (6) 477-485.

Edmond J.C. &Foroozan R. (2006) Cortical visual impairment in children. *Current Opinion in Ophthalmology*(17) 509-512.

Evenhuis H., van der Graaf G., Walinga M., Bindels-de Heus K., van Genderen M., Verhoeff M., Lantau K., van der Meulen-Ennema H., Meester N., Wienen L. & Schalij-Delfos N.(2007) Detection of Childhood Visual Impairment in At-Risk Groups. *Journal of Policy and Practice in Intellectual Disabilities* (4) 165–169.

Fantz R.L. (1965) Visual perception from birth as shown by pattern selectivity. *Annal of the New York Acadamy of Sciences* (118) 793-814.

Fazzi E., Bova S., Giovenzana A., Signorini S., Uggetti C. & Bianchi P. (2009) Cognitive visual dysfunctions in preterm children with periventricular leukomalacia. *Developmental Medicine and Child Neurolology* (51) 974-981.

Fazzi E., Signorini S.G., Bova S.M., La Piana R., Ondei P., Bertone C., Misefari W.& Bianchi P.E. (2007) Spectrum of visual disorders in children with cerebral visual impairment. *Journal of Child Neurology* (22) 294-301.

Fiorentini A., Berardi N., Falsini B. & Porciatti V. (1992) Interhemispheric transfer of visual perceptual learning in callosal agenesis. *Clinical Vision Sciences* (7) 133-141.

Fischer B, Biscaldi M, Gezeck S. (1997) On the development of voluntary and reflexive components in human saccade generation. *Brain Research* (754) 285-297.

Forsyth, L. (2008). *SIGN 50*.

Fukushima J., Hatta T. & Fukushima K. (2000) Development of voluntary control of saccadic eye movements I. Age-related changes in normal children. *Brain & Development* (22) 173-180.

Good W.V., Jan J.E., Desa L., Barrovich A.J., Groenveld M. & Hoyt C.S.(1994) Cortical visual impairment in children. *Survey of Ophthalmology* (38) 351-364.

Goodale M.A. & Milner A.D. (1992) Separate visual pathways for perception and action. *Trends in Neurosciences* (15) 20-25.

Gredebäck G., von Hofsten C. & Boudreau J.P. (2004) Infants' evolving representation of moving objects between 6 and 12 months of age. *Infancy* (6) 165-184.

Gredebäck G., Örnkloo H. & van Hofsten C. (2006) The development of reactive saccade latencies. *Experimental Brain Research* (173) 159-164.

Grinter E.J., Maybery M.T. & Badcock D.R. (2010) Vision in developmental disorders: Is there a dorsal stream deficit? *Brain Research Bulletin* (82)147-160.

Gunn A., Cory E., Atkinson J., Braddick O., Wattam-Bell J., Gizatta A. & Cioni G. (2002) Dorsal and ventral stream sensitivity in normal development and hemiplegia. *Neuroreport* (13) 843-847.

Haberecht M.F., Menon V., Warsofsky I.S., White C.D., Dyer-Friedman J., Glover G.H., Neely E.K. & Reiss A.L. (2001) Functional neuro anatomy of visuo-spatial working memory in Turner syndrome. *Human Brain Mapping* (14) 96-107.

Hertle R.W., Maldanado V.K., Maybodi M. & Yang D. (2002) Clinical and ocular motor analysis of the infantile nystagmus syndrome in the first 6 months of life. *British Journal of Ophthalmology* (86) 670-675.

Herweh C., Akbar M., Wengenroth M., Blatow M., Mair-Walther J., Rehbein N., Nennig E., Schenk J.P., Heiland S. & Stippich C. (2009) DTI of commissural fibers in patients with Chiari II-malformation. *Neuroimage* (44) 306-311.

Houben M.J., Goumans J. & van der Steen J. (2006) Recording three dimensional eye movements: scleral search coils versus video oculography. *Investigative Ophthalmology and Visual Science* (47) 179-87.

van den Hout B.M., de Vries L.S., Meiners L.C., Stiers P., van der Schouw Y.T., Jennekens-Schinkel A., Wittebol-Post D., van der Linde D., Vandenbussche E. & van Nieuwenhuizen O. (2004) Visual perceptual impairment in children at 5 years of age with perinatal haemorrhagic or ischaemic brain damage in relation to cerebral magnetic resonance imaging. *Brain and Development* (26) 251-261.

Huo R., Burden S.K., Hoyt C.S. & Good W.V. (1999) Chronic cortical visual impairment in children: aetiology, prognosis, and associated neurological deficits. *The British Journal of Ophthalmology* (83) 670-675.

Jacobs R., Anderson V. & Harvey A.S. (2001) Neuropsychological profile of a 9-year-old child with sub cortical band heterotopia or 'double cortex'. *Developmental Medicine and Child Neurology* (43) 628-633.

Jacobson L.K. & Dutton G.N. (2000) Periventricular leukomalacia: an important cause of visual and ocular motility dysfunction in children. *Survey of Ophthalmology (45)* 1-13.

Kavsek M., Yonas A. & Granrud C.E. (2012) Infants' sensitivity to pictorial depth cues: a review and meta-analysis of looking studies. *Infant Behavior and Development* (35) 109-128.

Kesler S.R., Haberecht M.F., Menon V., Warsofsky I.S., Dyer-Friedman J., Neely E.K. & Reiss A.L. (2004) Functional neuro anatomy of spatial orientation processing in Turner syndrome. *Cerebral Cortex* (14) 174-180.

Khetpal V. & Donahue S.P. (2007) Cortical visual impairment: etiology, associated findings, and prognosis in a tertiary care setting. *Journal of Aapos* (11) 235-239.

Kobayashi M., Otsuka Y., Nakato E., Kanazawa S., Yamaguchi M.K. & Kakigi R. (2012) Do infants recognize the Arcimboldo images as faces? Behavioral and near-infrared spectroscopic study. *Journal of Experimental Child Psychology* (111)22-36.

Koch C. & Ullman S. (1985) Shifts in selective visual attention: towards the underlying neural circuitry. *Human Neurobiology* (4)219-227.

Kwok S.K., Ho P.C., Chan A.K., Gandhi S.R. & Lam D.S. (1996) Ocular defects in children and adolescents with severe mental deficiency. *Journal of Intellectual Disability Research* (40) 330-335.

Le S., Cardebat D., Boulanouar K., Henaff M.A., Michel F., Milner D., Dijkerman C., Puel M. & Demonet J.F. (2002) Seeing, since childhood, without ventral stream: a behavioral study. *Brain* (125) 58-74.

Lewis T.L., Ellemberg D., Maurer D., Dirks M., Wilkinson F. & Wilson H.R. (2004) A window on the normal development of sensitivity to global form in Glass patterns. *Perception* (33)409-418.

Livingstone M. & Hubel D. (1988) Segregation of form, color, movement, and depth: anatomy, physiology, and perception. *Science NY* (240)740-749.

McCulloch D.L., Orbach H. & Skarf B. (1999) Maturation of the pattern-reversal VEP in human infants: a theoretical framework. *Vision Research* (39) 3673–3680.

Mercuri E., Baranello G., Romeo D.M.M., Cesarini L. & Ricci D. (2007) The development of vision. *Early Human Development* (83) 795–800.

Morrone M.C., Guzzetta A., Tinelli F., Tosetti M., Del Viva M., Montanaro D., Burr D. & Cioni G. (2008) Inversion of perceived direction of motion caused by spatial under sampling in two

children with periventricular leukomalacia. *Journal of Cognitive Neuroscience* (20) 1094-1106.

Noguchi T., Yoshiura T., Hiwatashi A., Togao O., Yamashita K., Nagao E., Uchino A., Hasuo K., Atsumi K., Matsuura T., Kuroiwa T., Mihara F., Honda H. & Kudo S. (2010) CT and MRI findings of human herpes virus 6-associated encephalopathy: comparison with findings of herpes simplex virus encephalitis. *American Journal of Roentgenology* (194) 754-760.

Noton D. & Stark L. (1971a) Eye movements and visual perception. *Scientific American* (224) 35-43.

Noton D. & Stark L. (1971b) Scan paths in eye movements during pattern perception. *Science* (171) 308-311.

Oliveira L.F., Simpson D.M. & Nadal J. (1996) Calculation of area of stabilometric signals using principal component analysis. *Physiological Measurement* (17) 305–312.

Palomares M., Pettet M., Vildavski V., Hou C. & Norcia A. (2010) Connecting the dots: how local structure affects global integration in infants. *Journal of Cognitive Neuroscience* (22) 1557-1569.

Panos P.T., Porter S.S., Panos A.J., Gaines R.N. & Erdberg P.S. (2001) An evaluation of a case of agenesis of the corpus callosum with Rourke's nonverbal learning disorder model. *Archives of Clinical Neuropsychology* (16) 507-521.

Pavlova M., Bidet-Ildei C., Sokolov A.N., Braun C. & Krageloh-Mann I. (2009) Neuromagnetic response to body motion and brain connectivity. *Journal of Cognitive Neuroscience* (21) 837-846.

Parrish E.E., Giaschi D.E., Boden C. & Dougherty R. (2005) The maturation of form and motion perception in school age children. *Vision Research* (45) 827-837.

Pavlova M., Sokolov A. & Krageloh-Mann I. (2007) Visual navigation in adolescents with early periventricular lesions: knowing where, but not getting there. *Cerebral Cortex* (17) 363-369.

Pel J.J.M, Manders J.C. & van der Steen J. (2010) Assessment of visual orienting behavior in young children using remote eye tracking: methodology and reliability. *Journal of Neuroscience Methods* (189) 252-256.

Pel J.J.M., van der Does J.M.E., Boot F.H., de Faber J.T., van der Steen-Kant S.P., Willemsen S.P. & van der Steen J. (2011) Effects of visual processing and congenital nystagmus on visually guided ocular motor behavior. *Developmental Medicine and Child Neurology* (53)344-349.

Pike M.G., Holmstrom G., de Vries L.S., Pennock J.M., Drew K.J., Sonksen P.M. & Dubowitz L.M. (1994) Patterns of visual impairment associated with lesions of the preterm infant brain. *Developmental Medicine and Child Neurology* (36) 849-862.

Purves D., Augustine G.J., Fitzpatrick D., Hall W.C., LaMantia A.S., McNamara J.O. & White L.E. (2012) *Neuroscience 5*th edition 229-275.

Reiss A.L., Freund L., Plotnick L., Baumgardner T., Green K., Sozer A.C., Reader M., Boehm C. & Denckla M.B. (1993) The effects of X monosomy on brain development: monozygotic twins discordant for Turner's syndrome. *Annals of Neurology* (34) 95-107.

Reiss A.L., Mazzocco M.M., Greenlaw R., Freund L.S. & Ross J.L. (1995) Neurodevelopmental effects of X monosomy: a volumetric imaging study. *Annals of Neurology* (38) 731-738.

Riddoch M.J. & Humphreys G.W. (1993) BORB: The Birmingham Object Recognition Battery. *Hove, UK: Lawrence Erlbaum Associates Ltd.*

Roberts M.A., Manshadi F.F., Bushnell D.L. & Hines M.E. (1995) Neurobehavioral dysfunction following mild traumatic brain injury in childhood: a case report with positive findings on positron emission tomography (PET). *Brain Injury* (9)427-436.

Rosander K, von Hofsten C. (2002) Development of gaze tracking of small and large objects. *Experimental Brain Research* (146) 257-264.

Rosen A.C., Rao S.M., Caffarra P., Scaglioni A., Bobholz J.A. & Woodley S.J. (1999) Neural basis of endogenous and exogenous spatial orienting: a functional MRI study. *Journal of Cognitive Neuroscience* (11) 135-148.

Ross G., Boatright S., Auld P.A. & Nass R. (1996) Specific cognitive abilities in 2-year-old children with subependymal and mild intraventricular hemorrhage. *Brain and Cognition* (32) 1-13.

Roucoux A., Culeea C. & Roucoux M. (1983) Development of fixation and pursuit eye movements in human infants. *Behavioral Brain Research* (10) 133–139.

Salati R., Borgatti R., Giammari G. & Jacobson L. (2002) Oculomotor dysfunction in cerebral visual impairment following perinatal hypoxia. *Developmental Medicine and Child Neurology* (44) 542-550.

Sandfeld Nielsen L., Skov L. & Jensen H. (2007) Visual dysfunctions and ocular disorders in children with developmental delay. II. Aspects of refractive errors, strabismus and contrast sensitivity. *Acta Ophthalmologica Scandinavica* (85) 419-426.

Sandfeld Nielsen L., Jensen H. & Skov L. (2008) Risk factors of ophthalmic disorders in children with developmental delay. *Acta Ophthalmologica Scandinavica* (86) 877–881.

Sestieri C., Pizzella V., Cianflone F., Romani G.L. & Corbetta M. (2008) Sequential activation of human oculomotor centres during planning of visually guided eye movements: a combined fMRI-MEG study. *Frontiers in Human Neuroscience* (1) 1-8.

Simon T.J., Bish J.P., Bearden C.E., Ding L., Ferrante S., Nguyen V., Gee J.C., McDonald-McGinn D.M., Zackai E.H. & Emanuel B.S. (2005) A multilevel analysis of cognitive dysfunction and psychopathology associated with chromosome 22q11.2 deletion syndrome in children. *Development and Psychopathology* (17) 753-784.

Simonsz H.J., Florijn R.J., van Minderhout H.M., Bergen A.A. & Kamermans M. (2009) Nightblindness-associated transient tonic down gaze (NATTD) in infant boys with chin-up head posture. *Strabismus* (17) 158-164.

Sommer M.A. & Wurtz R.H. (2008) Brain Circuits for the Internal Monitoring of Movements. *Annual Review of Neuroscience* (31) 317-338.

Spencer J., O'Brien J., Riggs K., Braddick O., Atkinson J. &Wattam-Bell J. (2000) Motion processing in autism: evidence for a dorsal stream deficiency. *Neuroreport* (11) 2765-2767.

van Splunder J., Stilma J.S., Bernsen R.M. &Evenhuis H.M. (2006) Prevalence of visual impairment in adults with intellectual disabilities in the Netherlands: cross-sectional study. *Eye* (20) 1004-1010.

Stiers P., van den Hout B.M., Haers M., Vanderkelen R., de Vries L.S., van Nieuwenhuizen O. & Vandenbussche E. (2001). The variety of visual perceptual impairments in pre-school children with perinatal brain damage. *Brain and Development* (23) 333-348.

Stiers P., Vanderkelen R., Vanneste G., Coene S., De Rammelaere M. & Vandenbussche E. (2002) Visual-perceptual impairment in a random sample of children with cerebral palsy. *Developmental Medicine and Child Neurology* (44) 370-382.

Stiers P., Swillen A., De Smedt B., Lagae L., Devriendt K., D'Agostino E., Sunaert S. & Fryns A. P. (2005). Atypical neuropsychological profile in a boy with 22q11.2 Deletion Syndrome. *Child Neuropsychology* (11) 87-108.

Stoelhorst G.M., Rijken M., Martens S.E., Brand R., den Ouden A.L., Wit J.M. & Veen S. (2005) Changes in neonatology: comparison of two cohorts of very preterm infants (gestational age <32 weeks): the Project On Preterm and Small for Gestational Age Infants 1983 and the Leiden Follow-Up Project on Prematurity 1996-1997. *Pediatrics* (115) 396-405.

Sturm V., Cassel D. & Eizenman M. (2011) Objective estimation of visual acuity with preferential looking*. Investigative Ophthalmology & Visual Science* (52)708-713.

Swaminathan M. (2011) Cortical visual impairment in children – a new challenge for the future? *Oman Journal of Ophthalmology* (4) 1-2.

Tatler B.W., Hayhoe M.M., Land M.F., Ballard D.H. (2011) Eye guidance in natural vision: Reinterpreting salience. *Journal of Vision* (11) 1-23.

Teller D.Y. (1979) The forced-choice preferential looking procedure: a psychophysical technique for use with human infants. *Infant Behavior & Development* (2) 135–153.

Tewes U., Rossmann P. & Schallberger U. (2001) HAWIK-III: HAmburg-Wechsler-Intelligenztest fur Kinder-Dritte Auflage. Manual; Ubersetzung und Adaptation der WISC-III Wechsler Intelligence Scale for Children. *Bern: von David Wechsler/The Psychological Corporation* (3rd ed.) 339.

Treue S. (2003) Visual attention: the where, what, how and why of saliency. *Current Opinion in Neurobiology* (13) 428-432.

Trobe J.D. (2001) The neurology of vision. *New York: Oxford university press* Chapter 1.

Ungerleider L.G. & Mishkin M. (1982) Two cortical visual systems. *Analysis of Visual Behavior, Cambridge: MIT press* (chapter 18) 549-586.

Valtonen J., Dilks D.D. & McCloskey M. (2008) Cognitive representation of orientation: a case study. *Cortex* (44) 1171-1187.

Vervloed M., Jansen N. & Knoors H. (2006) Visual rehabilitation of children with visual impairments. *Developmental and Behavioral Pediatrics* (27) 493-506.

Volpe J.J. (2001) Neurobiology of periventricular leukomalacia in the premature infant. *Pediatric Research* (50) 553-562.

Walter E., Mazaika P.K. & Reiss A.L. (2009) Insights into brain development from neurogenetic syndromes: evidence from fragile X syndrome, Williams syndrome, Turner syndrome and velocardiofacial syndrome. *Neuroscience* (164) 257-271.

Warburg M. (2001) Visual impairment in adult people with intellectual disability: literature review. *Journal of Intellectual Disability Research* (45) 424-438.

Wattam-Bell J., Birtles D., Nystrom P., von Hofsten C., Rosander K., Anker S., Atkinson J. & Braddick O. (2010) Reorganization of global form and motion processing during human visual development. *Current Biology* (20) 411-415.

Woodcock R. & Mather N. (1989) Woodcock-Johnson tests of cognitive ability: standard and supplemental batteries. *San Antonio: DLM Teaching Resources.*

Wurtz R.H. &Goldberg M.E. (1971) Superior colliculus cell responses related to eye movements in awake monkeys. *Science* (8) 82-84.

Yang Q., Bucci M.P. & Kapoula Z. (2002) The latency of saccades, vergence, and combined eye movements in children and in adults. *Investigative Ophthalmology and Visual Science* (43) 2939-2949.

Yarbus A.L. (1967) Eye movements and vision. *New York: Plenum Press*.

Summary

Summary

Chapter 1

Children with intellectual disabilities are expected to have an increased risk of visual processing dysfunctions due to their brain damage or brain development disorder. Ocular pathology is not necessarily present, which ophthalmologists define as Cerebral Visual Impairment (CVI). Within CVI, the higher visual functions that lead to perception can be affected. Examples of higher visual functions are the detection of motion, recognition of form, and spatial orientation. Current diagnostics of higher visual dysfunctions, and thus CVI, include neuropsychological test methods. A disadvantage of these test methods is that they require a developmental level of approximately four years for children to accomplish the test. This means that children with an intellectual disability, but also typically developing children <4 years, cannot be assessed for higher visual dysfunctions. Diagnosis in these groups of children is based on observations or based on exclusion, if no other explanation can be found for their visual impairment. As a result, the prevalence of CVI in children with intellectual disabilities remains unknown and is probably underestimated. Children may therefore not receive correct visual support and rehabilitation.

In current clinical practice, observation of eye movements is a direct method to study visual information processing and ocular motor quality. Delayed visual processing time to initiate an eye movement may relate to an increased risk of CVI. This means that assessment of eye movements can be used as a screening method for CVI. However, these observations depend on the experience of the professional and do not provide a quantitative outcome. For this thesis, an automatic remote eye tracker is used to objectively measure eye movements and to quantify visual orienting responses in terms of reaction time and fixation accuracy. Several visual stimuli are presented on a monitor while infrared cameras detect the eye movements of the child sitting in front of it. Our method does not require difficult instructions, assignments, or verbal responses, which makes it possible to assess children <4 years and children with intellectual and/or motor disabilities. A quantitative outcome allows us to compare visual orienting responses between children and within a group of children. In addition, these outcomes can be used for follow-up of visual training and rehabilitation.

The main objective of this thesis was to obtain the outcome parameters reaction time and fixation accuracy with the automatic remote eye tracker in a typically developing control group, and subsequently use the method to quantify visual information processing in children with intellectual disabilities.

Chapter 2

To understand visual processing at a more fundamental level, chapter 2 provides a systematic review of literature to find correlations between the etiology of brain damage, the location of brain damage, and higher visual dysfunctions. The main conclusion of this review is that the present status of research in the field of CVI does not allow to correlate between structural damage and its effect on cerebral visual processing dysfunctions. The small number of scientific studies in this research field and the lack of objective test methods could be a limiting factor. This outcome raises the question if, in view of the variability in structural damage, the diagnosis of CVI should not be based on anatomical markers only but on a more functional level. A separate description of the types of visual dysfunctions at a young age could provide a good starting point for specific daily support and rehabilitation, which may improve the general development of a child.

Chapter 3

In chapter 3 we assessed different groups of children with the remote eye tracking method: children with a (likely) diagnosis of CVI, children with congenital nystagmus only, and a healthy control group. The aim of this study was to investigate if these groups of children show different visual orienting responses. Visual orienting responses were quantified in terms of reaction time to fixation as the outcome parameter to quantify visual processing, and gaze fixation area as a measure of fixation quality. Children with CVI showed a significant prolonged visual processing time compared to the control group and children with congenital nystagmus. Low fixation quality was significant related to nystagmus. The overall conclusion of this study shows that parameter values collected with the remote eye tracking method are sensitive enough to distinguish between normal visual processing, impaired visual processing, and ocular motor disorders such as nystagmus.

Chapter 4

In this chapter, we focused on visual processing of coherent form and coherent motion, as these functions can serve as indicators for the performance of the ventral and dorsal stream respectively, two distinct cortical visual networks that process higher visual functions. Reaction time to fixation of coherent form and motion was calculated in typically developing children aged 0-12 years and in an adult group to assess developmental trends of coherent form and motion processing. We found that visual processing of the coherent form stimulus developed until the age of six years and of the coherent motion stimulus until eight years. Our results suggest that maturation of coherent form and motion processing follow different timelines, which corresponds with former studies using neuropsychological test methods in children >4 years. An important

conclusion from this chapter is that the quantification of visual orienting responses can be used to assess the quality of form and motion processing in children aged 0-12 years old.

Chapter 5

Three different visual stimuli were analyzed in this chapter, denoted as the cartoon, the form, and the motion stimulus. The quantification of typical visual orienting responses to these stimuli in the healthy control group was used as a reference for children with brain dysfunction, and in our case children with developmental and/or intellectual disabilities as the risk group. For each visual stimulus, a reference area of the reaction time to fixation as a function of age was calculated. The results showed that a majority of the children in our risk group did not score within the reference area and had a delayed visual processing time of one or more of the presented stimuli. The results of this study indicate that children with developmental and/or intellectual disabilities have a high risk of visual processing dysfunctions, possibly in combination with ocular motor disorders.

Chapter 6

Although we have shown that children with intellectual disabilities have an increased risk of visual processing dysfunctions, it would be of additional value to investigate which risk factors within this group of children are related to abnormal visual orienting responses. For this reason we studied if children's characteristics (age, gender, level of intellectual disability, mobility, gestational age, cerebral palsy, Down syndrome, visual acuity, strabismus, nystagmus, and epilepsy) were related to a delayed visual processing time and/or poor fixation quality. We found that age, level of intellectual disability, and Down syndrome significantly affected visual processing time of the cartoon stimulus. Ocular motor pathology significantly affected fixation quality during the presentation of the cartoon stimulus, but did not necessarily affected visual processing time. This chapter indicates that visual processing of such a stimulus takes more time for low IQ children and that risk factors of visual processing dysfunctions may exist within children with intellectual disabilities.

Conclusion

The work presented in this thesis should make us aware of the increased risk of higher visual processing dysfunctions in children with developmental and/or intellectual disabilities and that a variety of visual dysfunctions may exist within this group. Our advice to clinical practice is that all children with developmental and/or intellectual disabilities should be screened at a young age for different types of higher visual processing dysfunctions and if needed referred to a rehabilitation center for low vision. True validation of the remote eye tracking method can be achieved if the

outcomes of the eye tracker based methodology are compared with current neuropsychological test methods in a control group of children who are capable to perform both test methods correctly. Instead of labeling a child with the very broad diagnosis of CVI by exclusion, it may become possible to diagnose specific higher visual processing dysfunctions. A separate description of the different types of visual dysfunctions within one child could be useful and a good addition in clinical practice.

Samenvatting

Samenvatting

Hoofdstuk 1

Bij kinderen met een verstandelijke beperking verwacht je een verhoogd risico op visuele verwerkingsproblemen door hun hersenschade of hersenontwikkelingsstoornis. Hierbij hoeft er op oogheelkundig niveau geen pathologie aanwezig te zijn, wat in de huidige kliniek cerebrale visuele inperking (CVI) wordt genoemd. CVI kan tot uiting komen in stoornissen van de visuele functies die leiden tot perceptie, de zogenoemde hogere visuele functies. Voorbeelden van hogere visuele functies zijn het detecteren van beweging, het herkennen van vormen en ruimtelijke oriëntatie. Huidige diagnostiek van hogere visuele dysfuncties, en dus CVI, vindt plaats door middel van neuropsychologische testmethodes. Het nadeel van deze testmethodes is dat zij alleen inzetbaar zijn bij kinderen met een ontwikkelingsleeftijd >4 jaar. Dit betekent dat hogere visuele functies bij kinderen met een verstandelijke beperking, maar ook bij gezonde kinderen <4 jaar met een typische ontwikkeling, tot op heden niet of moeilijk getest kunnen worden. De diagnostiek bij deze doelgroepen vindt hierdoor plaats op basis van observaties en op basis van exclusie, wanneer er geen andere verklaring voor de visuele problematiek kan worden gevonden. Het gevolg is dat de prevalentie van CVI in deze groepen waarschijnlijk onderschat wordt en dat kinderen mogelijk niet de juiste visuele ondersteuning en stimulatie krijgen.

In de huidige praktijk is het bestuderen van oogbewegingen en kijkgedrag een directe manier om visuele verwerking en oogmotoriek te beoordelen. Een vertraagde visuele verwerking wordt als een verhoogd risico op CVI gezien en het beoordelen van oogbewegingen kan dus worden gebruikt als een screeningsmethode voor CVI. Het nadeel is echter dat dit is gebaseerd op observaties zonder kwantitatieve uitkomstmaat. Voor dit proefschrift wordt er daarom voor het eerst gebruik gemaakt van een geautomatiseerde methode, waarbij oogbewegingen objectief worden gemeten. Op een tv scherm worden visuele stimuli gepresenteerd, terwijl infrarood camera's de oogbewegingen detecteren. Instructies en feedback van de deelnemer zijn niet nodig, waardoor ook kinderen met een verstandelijke beperking kunnen worden onderzocht. Met de nieuwe methodiek wordt het kijkgedrag van kinderen dus op een objectieve manier getest. Uit de gemeten oogbewegingen worden kwantitatieve uitkomstmaten berekend en kan kijkgedrag binnen en tussen groepen kinderen worden vergeleken. Ook kunnen deze uitkomsten als uitgangspunt worden gebruikt voor het evalueren van visuele training en therapie.

Hoofdstuk 2

Om visuele verwerking op fundamenteel niveau beter te begrijpen, werd er in hoofdstuk 2 op basis van een systematisch review gekeken of er correlaties zijn tussen de etiologie van de

hersenschade, de anatomische schade en het visueel functioneren. Op basis van de huidige literatuur is het niet mogelijk om hierin verbanden te leggen. Er blijkt nog te weinig wetenschappelijk onderzoek te zijn gedaan op dit specifieke gebied en vaak leveren de gebruikte testmethodes te beperkte informatie. De visuele verwerking in het brein is een (te) complex systeem, waarbij meerdere gebieden met elkaar in verbinding staan. Wij concluderen dat CVI niet gebaseerd zou moeten zijn op anatomische structuren, maar op functioneel niveau. Als men op jonge leeftijd al weet welke visuele functies zijn aangedaan, kan de juiste ondersteuning en gerichte visuele training mogelijk de ontwikkeling positief beïnvloeden.

Hoofdstuk 3

In hoofdstuk 3 werden verschillende groepen kinderen getest met de geautomatiseerde methode: kinderen met de (waarschijnlijkheids)diagnose CVI, kinderen met alleen aangeboren nystagmus en een gezonde controle groep. Hierdoor kon er onderzocht worden of er verschillen in kijkgedrag bestaan tussen kinderen met CVI, kinderen met stoornissen in de oogmotoriek en de gezonde controle groep. Uit de oogbewegingreacties werd de visuele verwerkingstijd uitgedrukt in de reactietijd tot fixatie. De kwaliteit van het fixeren werd uitgedrukt in een maat voor de grootte van het fixatiegebied. Kinderen met CVI laten een significant langere reactietijd tot fixatie zien in vergelijking tot de controle groep en kinderen met nystagmus. De kwaliteit van fixeren werd mede bepaald door het wel of niet hebben van nystagmus. Met deze studie is duidelijk gemaakt dat op basis van oogbewegingreacties onderscheid kan worden gemaakt tussen normale visuele verwerking, vertraagde visuele verwerking en stoornissen in de oogmotoriek.

Hoofdstuk 4

Nu er in hoofdstuk 3 is aangetoond dat de methode sensitief genoeg is om visuele verwerking bij verschillende groepen kinderen te kwantificeren, richtten wij ons in hoofdstuk 4 op twee typen hogere visuele functies: het verwerken van vorm en het verwerken van beweging. Deze visuele functies zijn gekozen omdat ze kunnen worden gebruikt als kwaliteitsindicatoren van twee in de literatuur beschreven corticale visuele verwerkingspaden van het brein, bekend als de ventrale (vorm) en dorsale (beweging) stroom. Op basis van de reactietijd tot fixatie van de vorm- en bewegingstimulus werd in hoofdstuk 4 de ontwikkeling van het visueel verwerken van vorm coherentie en beweging coherentie bij gezonde kinderen van 0-12 jaar en een groep volwassenen onderzocht. Het blijkt dat voor vorm de kinderen vanaf zes jaar oud vergelijkbare waardes van verwerking hebben als volwassenen. Voor het verwerken van beweging hebben we gevonden dat deze ontwikkeling langer doorloopt tot de leeftijd van acht jaar. Deze twee visuele functies volgen ieder dus een eigen ontwikkelingspad dat overeenkomt met voorgaand gepubliceerd onderzoek, waar deze ontwikkeling bij kinderen vanaf vier jaar werd onderzocht door middel van

neuropsychologische testmethodes. Uit ons onderzoek kan worden geconcludeerd dat het kwantificeren van kijkgedrag kan worden gebruikt om de kwaliteit van het verwerken van vorm en beweging te bepalen bij kinderen van 0-12 jaar oud.

Hoofdstuk 5

Het kwantificeren van het kijkgedrag voor drie verschillende visuele stimuli (cartoon, vorm en beweging) bij gezonde kinderen met een typische ontwikkeling (controle groep) werd in dit hoofdstuk gebruikt als referentiewaarde voor kinderen met een vorm van hersenschade of een hersenontwikkelingsstoornis (risicogroep). Voor elke visuele stimulus werd een referentiegebied voor de reactietijd tot fixatie als functie van leeftijd uitgerekend. Voor onze studie bestond de risicogroep uit kinderen met een ontwikkelingsstoornis en/of verstandelijke beperking van 2-14 jaar. De meerderheid van de risicogroep liet een vertraagde reactietijd zien naar één of meer stimuli ten opzichte van het referentiegebied. Dit maakt duidelijk dat we ons bewust moeten zijn van het verhoogde risico op visuele verwerkingsproblemen (mogelijk in combinatie met oogmotoriek stoornissen) bij kinderen met een ontwikkelingsstoornis en/of verstandelijke beperking.

Hoofdstuk 6

Hoewel we nu reeds inzicht hebben verkregen in de verhoogde prevalentie van visuele verwerkingsproblemen bij kinderen met een verstandelijke beperking, is het voor de praktijk van toegevoegde waarde om te weten welke risicofactoren binnen deze groep een voorspellende waarde hebben op hogere visuele dysfuncties. In hoofdstuk 6 werd onderzocht of de individuele eigenschappen van de kinderen in de risicogroep (leeftijd, geslacht, niveau van functioneren, mobiliteit, zwangerschapsduur, Cerebral Palsy, syndroom van Down, visus, strabismus, nystagmus en epilepsie), gerelateerd zijn aan een langere verwerkingstijd en/of verminderde kwaliteit van fixeren. Leeftijd, IQ en het syndroom van Down hadden een significante invloed op de visuele verwerkingstijd van de cartoon stimulus. Oculaire pathologie beïnvloedde significant de kwaliteit van het fixeren bij de cartoon stimulus, maar niet direct de visuele verwerkingstijd. Dit hoofdstuk laat zien dat een langere verwerkingstijd gerelateerd is aan een laag IQ en dat er binnen de groep kinderen met een verstandelijke beperking risicofactoren aanwezig kunnen zijn.

Conclusie

De resultaten van deze studie moeten ons doen beseffen dat er een verhoogd risico bestaat van visuele verwerkingsproblematiek bij kinderen met een ontwikkelingsstoornis en/of verstandelijke beperking en dat er een verscheidenheid aan visuele dysfuncties bestaat binnen deze groep. Deze

groep kinderen zou op jonge leeftijd al moeten worden gescreend en zo nodig naar onderzoekcentra voor slechtzienden worden verwezen voor verder onderzoek. Om de geautomatiseerde methode daadwerkelijk te valideren, moeten de uitkomsten worden vergeleken met de huidige neuropsychologische testmethodes bij kinderen die beide testen correct kunnen uitvoeren. In plaats van het kind te labelen met de brede diagnose CVI, wordt het in de toekomst misschien mogelijk om specifieke stoornissen van visuele functies te diagnosticeren. Het samenstellen van een visueel profiel, waarmee zoveel mogelijk visuele verwerkingsgebieden worden getest, kan van toegevoegde waarde zijn voor de huidige praktijk.

List of publications

List of publications

Pel J.J.M., van der Zee Y.J., Boot F.H., Evenhuis H.M., van der Steen J.
Remote eye tracking assesses age dependence processing of coherent motion in typically developing children.
Accepted for Journal of Medical Engineering & Technology; 2012

Boot F.H., Pel J.J.M., Vermaak M.P., van der Steen J. & Evenhuis H.M.
Delayed visual orienting responses in children with developmental and/or intellectual disabilities.
Accepted for Journal of Intellectual Disability Research; 2012 published online

Boot F.H., Pel J.J.M., Evenhuis H.M., van der Steen J.
Factors related to impaired visual orienting behavior in children with intellectual disabilities.
Research in Developmental Disabilities; 2012 (33) 1670-1676

Boot F.H., Pel J.J.M., Evenhuis H.M., van der Steen J.
Quantification of visual orienting responses to coherent form and motion in typically developing children aged 0-12 years.
Investigative Ophthalmology and Visual Science; 2012 (53) 2708-2714

Pel J.J.M., van der Does J.M.E., Boot F.H., de Faber J.T., van der Steen-Kant S.P., Willemsen S.P. & van der Steen J.
Effects of visual processing and congenital nystagmus on visually guided ocular motor behavior.
Developmental Medicine and Child Neurology; 2011 (53) 344-349.

Boot F.H., Pel J.J.M., van der Steen J.& Evenhuis H.M.
Cerebral Visual Impairment: which perceptive visual dysfunctions can be expected in children with brain damage? A systematic review.
Research in Developmental Disabilities; 2010 (31)1149-1159.

PhD Portfolio

PhD Portfolio

Name PhD student: F.H. Boot	PhD period: 2009-2012		
Department: General Practice & Neuroscience	Promotor: Prof.dr. H.M. Evenhuis		
Research School: Erasmus MC	Copromotor: Dr. J. Van der Steen & Dr.ir. J.M.M. Pel		
	Year	**Workload**	
		Hours	**ECTS**
1. PhD training			
General courses			
BROK (Basiscursus Regelgeving Klinisch Onderzoek)	2010	25	
Scientific writing	2010-2011		2
Seminars and workshops			
Lab talks & seminars department of Neuroscience	2009-2011		1
Helmholtz Lecture	2010	2	
Seminar series Intellectual Disability Medicine	2009-2011		1
NWO Talent day	2010	8	
PhD Day Erasmus MC	2010	8	
Lof der Geneeskunst	2009-2010	16	
Presentations			
Bessensap	2010		1
Young reserachers colloquium PMID Groningen	2010		1
2 presentations seminar Neuroscience	2009-2011		1
2 presentations seminar Intellectual disability medicine	2009-2011		1
(Inter)national conferences			
IASSID Rome & Halifax (oral presentation)	2010-2012		4
InZicht Ontmoetingsdag (poster presentation)	2010		1
Low Vision Kuala Lumpur (poster presentation)	2011		1
Dag van de Perceptie (poster presentation)	2011		1
CVRS (poster presentation)	2011		1
2. Teaching			
Lecturing / workshops			
Summer school Neuroscience	2009	4	
Workshop science day AVG physicians	2010		1
Workshop Masters Neuroscience	2010		1
Supervising practicals			
Practicals about the visual, ocular and vestibular system	2010-2011	50	
Supervising students			
Bachelor project Gezondheid & Leven	2010-2011	112	
Summer school student	2011	10	
Other			
Review manuscript IOVS journal	2010	8	
Review manuscript IJO journal	2011	8	
TOTAL		251	18

Curriculum Vitae

Curriculum Vitae

Fleur Heleen Boot werd geboren op 11 september 1981 in Redhill (Engeland). In 1999 behaalde zij haar VWO diploma aan het Geert Grote College te Deventer. Net een week 18 jaar, vertrok Fleur als "backpacker" voor 9 maanden naar Australië en Nieuw Zeeland. Terug in Nederland heeft zij een jaar Life, science & technology gestudeerd aan de Technische Universiteit Delft.

In 2001 is Fleur begonnen met haar studie geneeskunde aan de Erasmus Universiteit te Rotterdam. Haar keuze coschap chirurgie heeft zij in Ifakara, Tanzania gedaan en haar afstudeeronderzoek KNO in Manchester, Engeland. Na haar artsexamen op 19 december 2008, bleef de vraag voor haar; "welke weg sla ik in"? Een half jaar van onzekerheid en zelfonderzoek volgde. Het resulteerde in de wens en mogelijkheid om promotie onderzoek te doen aan het Erasmus MC te Rotterdam bij de afdeling Neurowetenschappen en Geneeskunde voor Verstandelijk Gehandicapten en opgeleid te worden als AVG (arts voor verstandelijk gehandicapten).

Momenteel werkt Fleur als arts-assistent bij Tragel Zorg in Clinge en zal in februari 2013 beginnen met haar opleiding. Om haar onderzoek kenbaar te maken, heeft Fleur deelgenomen aan verschillende congressen o.a. in Kuala Lumpur (KL Vision), Rome en Halifax (IASSID).

Fleur is mijn dochter. Ik weet vanuit mijn eigen (werk)ervaring dat er nog een wereld van onderzoek en ontwikkeling nodig is. Ik hoop dat zij daar een bijdrage aan kan leveren!

Ineke van Wijngaarden-Noordzij

Dankwoord

Dankwoord

Er zijn vele mensen die ik moet bedanken voor hun hulp en steun. Collega's, vrienden en familie, zonder deze basis ben je nergens. In het bijzonder wil ik mijn twee promotoren (Hans, dat ben jij toch ook echt voor mij) bedanken, die hun kennis hebben gebundeld voor dit onderzoeksgebied en waarbij de praktijk en wetenschap elkaar vinden. Heleen, je bent een pittige, maar ik heb op meerdere vlakken veel van je geleerd en heb respect voor wat jij allemaal hebt gedaan en bereikt op het gebied van geneeskunde voor mensen met een verstandelijke beperking. Hans, wat ben jij lief en behulpzaam geweest voor mij. En wat verdien jij het om hoogleraar te zijn!

Om het voor elkaar te krijgen een proefschrift daadwerkelijk binnen een bepaalde periode af te ronden zijn er drie aspecten van groot belang. Althans zo heb ik het ondervonden. Ten eerste moet je het in je hebben om efficiënt te zijn. Hiervoor dank ik mijn vader, aangezien hij deze genen aan mij heeft doorgegeven. Pap, je leert mij dat met intelligentie, eerlijkheid en daadkracht heel veel te bereiken is in het leven. Ten tweede heb je doorzettingsvermogen nodig. Het stukje dat ik hiervan heb, heb ik zeker van mijn moeder geërfd, ik ken namelijk niemand die zo dapper is als zij. Mam, door jou probeer ik altijd in oplossingen te denken en niet te oordelen over mensen en hun keuzes. Je geeft me het vertrouwen dat ik alles kan. Het derde aspect is denk ik nog het belangrijkste en dat is je dagelijkse begeleiding. Om in een goed tempo resultaten te begrijpen, te analyseren, te bediscussiëren en op te schrijven, wanneer dit iets nieuws voor je is en je hierin nog moet groeien, heb je een dagelijkse begeleider nodig met veel tijd en energie. Ik ben heel dankbaar dat dit voor mij Johan Pel was. Johan, ik wil je super bedanken voor al je hulp en intelligente ideeën. Zonder jou was het zeker niet gelukt. Je hebt mij altijd geholpen, je hebt mijn sterke punten leren kennen, je hebt open gestaan om mijn zwakke kanten te begrijpen, en je ziet altijd dat het glas halfvol is. Je hebt een enorm talent om mensen te enthousiasmeren, om iedereen van elk niveau iets te leren en dit met plezier te doen. Ik weet zeker dat je hier nog heel veel mee gaat bereiken!

Een promotie afronden naast je werk, bleek voor mij geen ideale situatie. Jeetje, wat kom je jezelf dan tegen. Gelukkig stond Tragel Zorg altijd achter dit proefschrift en hebben zij mij de tijd en vrijheid gegeven dit ook daadwerkelijk te kunnen afronden. En daarbij ik heb vooral het geluk gehad dat ik in deze periode Erlend heb leren kennen. Lief, door jou kon ik de zorgen in mijn hoofd relativeren en wat hou jij een goede spiegel bij mij voor, dank!