Brain & Development 41 (2019) 135–149

BRAIN & DEVELOPMENT
Official Journal of the Japanese Society of Child Neurology

www.elsevier.com/locate/braindev

Original article

Combining visual sensory functions and visuospatial orienting functions in children with visual pathology: A longitudinal study

Marlou J.G. Kooiker [a,*], Hélène J.M. Verbunt [b], Johannes van der Steen [a,b] Johan J.M. Pel [a]

[a] *Vestibular and Oculomotor Research Group, Dept. Neuroscience, Erasmus MC, Rotterdam, the Netherlands*
[b] *Royal Dutch Visio, Centre of Expertise for Partially Sighted and Blind People, Huizen, the Netherlands*

Received 31 October 2017; received in revised form 5 September 2018; accepted 18 September 2018

Abstract

Background: Peripheral and central visual processing development highly depends on the integrity of the visual sensory system and the allocation of visuospatial attention.

Method: We quantitatively followed visual sensory functions (VSF) and visuospatial orienting functions (VOF) over two years in 77 children (1–13 years) with different types of visual pathology.

Results: Within the clinical groups, VSF were relatively constant over two years, except visual acuity, and VOF were characterized by longer reaction time, shorter fixation duration, and lower fixation accuracy than normal for their age. Children with peripheral pathology had high rates of abnormal VSF, of changes to abnormal visual acuity at 1–6 years, and larger and more abnormal VOF (fixation inaccuracy). Children with central pathology had relatively good VSF, whereas two-third had delayed orienting reaction times that differed from other groups mainly at 1–6 years.

Conclusion: The distinct patterns of quantitative VSF and VOF over time between the visual pathology groups, and the finding that both methods provided complementary information, argues for combining both types of assessments to provide comprehensive monitoring of visual functioning in children from a young age.

Keywords: Visual sensory functions; Visual orienting functions; Visuospatial attention; Longitudinal study; Eye tracking; Peripheral visual pathology; Central visual pathology; Children

1. Introduction

The development of vision is one of the crucial factors that influences general development in childhood, underlying changes in motor, cognitive, learning and social interaction skills [1]. The use of visual information during development is mediated by a highly complex network that matures from before birth up to adolescence [2]. Anatomically, the visual system can roughly be divided into peripheral components (ocular structures and anterior pathways up to the thalamus), and central components (posterior pathways to primary visual and extrastriate cortices). The integrity of both components determines the processing of the different aspects of visual information and thereby the final quality of vision. Given the impact of visual impairments of either peripheral or central origin on other

* Corresponding author at: Erasmus Medical Center, Department of Neuroscience, PO Box 2040, 3000 CA Rotterdam, the Netherlands.
E-mail address: m.kooiker@erasmusmc.nl (M.J.G. Kooiker).

https://doi.org/10.1016/j.braindev.2018.09.006
0387-7604/

developmental areas, it is important to follow and monitor visual functioning in children with (a risk of) visual impairments.

In current clinical practice, e.g. visual rehabilitation centers, visual functioning of children with suspected visual impairments is assessed with orthoptic or visual function exams. These exams include visual sensory functions (VSF), such as visual acuity or visual field sensitivity, and oculomotor functions, such as ocular alignment and motility. During these exams a certain degree of attentiveness to the visual environment and the visual tests is needed from the child. The importance of such visuospatial attention orienting can be noticed in one of the best-established methods to nonverbally assess visual functioning in children: the preferential looking (PL) paradigm. In PL paradigms, a child's eye movement responses to visual targets are observed in order to grade the threshold level of detection of the targets and infer the corresponding level of visual function [3]. The reflexive, or bottom-up, allocation of attention and subsequent fixation of a visual target in the form of eye movements is necessary for visual information to enter the peripheral and central visual processing system. This means that these reflexive visuospatial orienting functions (VOF) are a crucial first step to further process visual information, leading to perception. However, at present this aspect of visual functioning is not assessed on a regular basis, and judgement of the characteristics of a child's reflexive eye movements during visuospatial attention orienting requires fast and accurate observation skills.

The increasing use of eye tracking systems in medical research in recent years has enabled a coupling of PL paradigms with the automated recording of eye movements, and this coupling in turn enables VOF measurements. Measuring VOF with an eye tracker has the advantage that performance is objectively recorded and can be quantitatively analyzed, while it does not rely on verbal communication or on behavioral observations. From those VOF recordings, high-resolution temporal and spatial characteristics, such as the timing, localization, and duration of orienting eye movements and fixations can be quantified. This allows an objective assessment of the quality of visuospatial attention allocation in PL settings [4]. Previous studies showed that VOF parameters are sensitive indicators for pathology in the visual system: the majority of children with visual pathology showed prolonged orienting reaction times to various visual stimuli and a more general fixation inaccuracy [5,6]. The prevalence of abnormal VOF was particularly high in children with (risk factors for) cerebral visual impairments (CVI) [6,7]. With regard to assessments over time, age-related developmental trajectories of orienting reaction times were established for typically developing children from 1 to 12 years, and it was found that the development of these reaction times was affected by both the age of a child and the salience of a presented visual PL stimulus [4].

Opposed to this normative developmental data, it is not yet known to what extent VOF performance changes over time in clinical groups of children with different types of visual pathology. This is in line with longitudinal cohort studies on VSF, which tend to be scarce in this population. A few studies in children with peripheral visual pathologies have reported relatively good prognoses in terms of visual acuity [8–12], whereas visual acuity outcomes were lower in subjects with neurological involvement [13,14]. A limitation of the available longitudinal studies is that outcome is only expressed in terms of visual acuity or contrast sensitivity, which comprise only a small part of all visual abilities that are relevant for daily visual performance. Therefore, these VSF should not be tested in isolation without considering more functional aspects of vision [15]. Combining VSF with VOF may add to the existing literature on visual development and may provide insight in strengths and weaknesses of visual performance over time in children with visual impairments, not only in terms of conventional visual functions but also from a more functional perspective by means of reflexive visuospatial attention orienting. This knowledge may greatly add to the understanding and management of visual function performance and prognosis in visual rehabilitation practice.

The aim of this study was to quantitatively follow visual sensory functions (VSF), and visuospatial orienting functions (VOF) in visually impaired children aged one to 12 years. We conducted a two-year longitudinal study in a population-based cohort of children with a heterogeneous range of visual impairments that were primarily caused by peripheral, central, or nonspecific visual pathology. The total group was divided in two age groups (1–6 and 7−12 years) to investigate differences in VSF and VOF results and development in children before and from school age. All children underwent VSF assessments (to examine visual sensory and oculomotor functions: visual acuity, contrast sensitivity, nystagmus, strabismus, ocular motility, stereovision, visual field, and color vision) and an eye tracking-based assessment of VOF. VOF were recorded in response to highly salient visual stimuli and characterized by three parameters: reaction time, fixation duration, and fixation accuracy, to capture the speed of reflexive attention orienting, and the duration and accuracy of subsequent target fixation, respectively. Both assessments were repeated after two years to document natural changes. We hypothesized that children with peripheral pathology would show more abnormalities in VSF, but relatively stable overall visual performance over two years, whereas children with central pathology would show more abnormalities in VOF and more overall changes in visual performance over two years.

2. Methods

2.1. Participants

The study population consisted of 119 children with visual impairments who were clients of Royal Dutch Visio, a visual advisory and rehabilitation center in the Netherlands. Prior to the start of the study, written informed consent was obtained from the parents of all children. This study adhered to the tenets of the Declaration of Helsinki. Data collection took place from May 2012 to February 2015. Children were included by psychologists when the following criteria were met: (1) calendar age from one to 12 years (at date of inclusion), and (2) confirmed or suspected visual impairments, based on World Health Organization criteria or due to neurologic vision loss [16,17]. Children were excluded when they had a visual acuity <0.05 (3/60 Snellen acuity) or when they had oculomotor apraxia. Data for the current study were obtained longitudinally at a baseline measurement and at a two-year follow-up measurement. 119 children were included in the first year and 89 children had a two-year follow-up appointment. Sixteen children dropped out due to logistics, illness or hospital admission, and 14 children because they no longer were clients of Royal Dutch Visio. The age and type of diagnosis of the children who dropped out did on average not differ from the included children. Of the 89 children, in 12 children we could not collect enough gaze data for analysis on one or more occasions (i.e., less than 25% of data), due to absence of visual attention to the monitor (N = 10), or ocular pathology that was incompatible with the corneal-reflection eye tracking technique (i.e., aniridia; N = 2). 13 children were excluded because they had a progressive visual disorder for which naturally occurring changes over two years could not reliably be assessed. The mean age of the total clinical group (N = 64) was 8.1 years (range 1.6 to 12.7 y) at inclusion. Children were divided in two groups based on age: a young group (N = 17; mean age (SD) = 4.9(1.2) years), and an older group (N = 47; mean age(SD) = 9.2(1.5) years). Children in the clinical group were divided in four groups, according to the underlying primary pathology of their visual impairments: peripheral (N = 24), central (N = 29), or nonspecific (N = 11). Peripheral pathology was defined as a pre-geniculate cause of visual impairment, and central pathology was defined as primary damage to retro-geniculate pathways or visual cortex. Nonspecific pathology implied apparent visual problems, but without structural anatomical evidence (for a classification see Table A1).

2.2. Procedure

At baseline and after two years, all children in the risk group underwent a VSF assessment and an eye tracking-based assessment of VOF, and their medical records were examined.

The VSF assessments were performed by experienced orthoptists and optometrists of Royal Dutch Visio. All examiners adhered to a standardized test protocol to ensure similar scoring of the visual sensory and oculomotor functions (see Table A2). This protocol was designed in collaboration with the orthoptists, to ensure uniform assessments that were suitable for the child's developmental age and that adhered to best clinical practice. Whenever possible and available, quantitative tests were used. Whether the scoring of performance was done quantitatively or qualitatively depended on age of the children and relevance for clinical practice. Therefore, the following functions were qualitatively scored: nystagmus, strabismus, ocular motility, stereovision, visual field and color vision. The functions near visual acuity and contrast sensitivity were quantitatively scored. In Table A2 the used tests and the scoring method are specified per function.

Within one month before or after the VSF assessment, VOF were assessed with a remote eye tracking system. This system consisted of a 24-inch monitor with integrated infrared cameras that was used to record the eye movements during the presentation of various visual stimuli (Tobii T60XL; Tobii Corporation, Danderyd, Sweden). The system used cornea reflection, compensated for head movements, and sampled at 60 Hz with a system latency of ~30 ms. Children were situated at ~60 cm distance from the monitor. The monitor was attached to a swing arm and was positioned perpendicular to the child's eyes to ensure a good pupil signal. Depending on the children's physical abilities they were seated either independently, in a wheelchair, or in a pram. No specific instructions were given prior to starting the test. Stimulus presentation was designed according to a four-alternative preferential looking paradigm, in which stimuli were shown in one of four monitor quadrants (i.e., target areas) against a non-patterned background. Each stimulus was placed in one of the quadrants and a circular target area was defined with a diameter of 6 degrees of visual angle. Reflexive eye movement responses to these target areas were measured. A set of various visual stimuli was used, but for the present study we only analyzed cartoon stimuli: highly-salient short movies containing color, motion, form and contrast (Fig. 1, panel A). Such stimuli trigger fast reflexive eye movement responses in children with and without visual impairments [6,18] and are suited to provide an indication of visuospatial attention orienting. The cartoon stimuli were presented for ten seconds each, four times in each of the four monitor quadrants, for a total of 16 trials. All stimuli were presented in a randomized manner, and total assessment duration (all stimuli included) was ~ten minutes.

From the medical records, data were gathered about the following clinical factors at baseline: diagnosis,

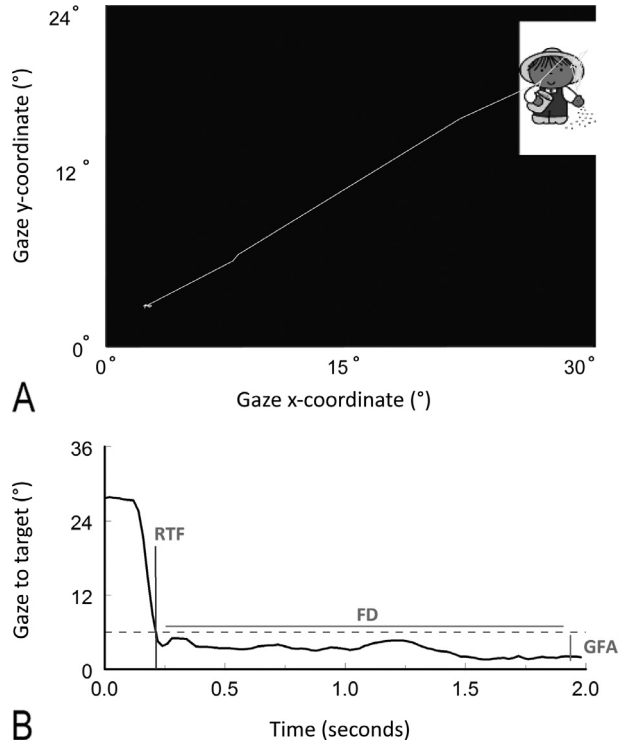

Fig. 1. Panel A shows the Cartoon stimulus, with superimposed an eye movement (solid line) to the target area. In panel B, the orienting eye movement to the target area of the Cartoon stimulus (i.e., the VOF) is visualized, with markers indicating the three VOF parameters: reaction time to fixation (RTF), gaze fixation area (GFA), and fixation duration (FD).

adverse childhood events (preterm birth, presence of brain abnormalities), clinical diagnosis of cerebral visual impairment (CVI; i.e., a diagnosis established by a multidisciplinary team), intellectual disability, visual perception dysfunctions, and behavioral disorders (see Table A1 for classifications). At the follow-up measurement, newly available information on visual and overall function was added to the database: e.g., acquired brain damage or ocular disease, the occurrence of surgical procedures, or visual interventions.

2.3. Data analysis

2.3.1. Scoring of VSF parameters

The visual sensory and oculomotor functions were assessed binocularly with the standardized protocol at baseline and at follow-up (see Table A2 for the scoring criteria per function). Quantitative outcomes were only provided for contrast sensitivity and visual acuity; for the other functions detailed qualitative outcomes were given. Visual acuity was expressed on a decimal scale that corresponded with one line on visual acuity charts and contrast sensitivity was expressed as the minimum level of contrast difference that could be resolved. Second, all functions were denoted as normal or abnormal, according to the child's developmental age and the norms of the used tests (Table A2). Abnormal performance indicated a dysfunction.

2.3.2. Longitudinal analysis of VSF

Changes over two years were only calculated for the two quantitatively measured functions: visual acuity and contrast sensitivity, since the qualitative (i.e., normal/abnormal) classifications of the other functions were quite broad and therefore not expected to spontaneously change over the relatively short period of two years. First, we assessed the average performance at baseline and at follow-up and calculated the absolute changes in visual acuity and contrast sensitivity, separately for the groups with peripheral, central, nonspecific and progressive visual pathology. Second, at both time points, the number of children with normal and abnormal performance for their age were denoted per function. Two-year changes in visual acuity and contrast sensitivity were expressed as 'changed to normal' (from abnormal in the first year to normal two years later), 'changed to abnormal' (from normal in the first year to abnormal two years later), or no change over two years.

2.3.3. Calculation of VOF parameters

We manually analyzed the eye movement responses to all presented stimuli using a self-written software program in MATLAB (Mathworks Inc., Natick, MA, USA). Firstly, we calculated the visual angle between the point of gaze and the stimulus location during the first two seconds of each Cartoon presentation, using the average viewing distance. The visual angle, i.e. the distance, between the point of gaze and the center of the target area over time was plotted for visual inspection (Fig. 1, panel B). During this inspection, we assessed for each stimulus presentation if the child had seen it by using the plotted eye movement data and the following set of criteria. A stimulus was classified as 'seen' when there was a saccadic eye movement within the first two seconds of stimulus presentation towards the center of the target area, when the eyes stayed at least 300 ms in the target area, when the eyes were not in the target area from the start of a trial, and when there were no gaps larger than 200 ms in the eye movement data. When one or more of these criteria were not met, the stimulus presentation was classified as 'unseen' and was not included for further analysis. Next, for all stimulus presentations that were classified as 'seen', we calculated three VOF parameters (visualized in Fig. 1, panel B). Averages of these parameters per child were only included for analysis when they could be calculated for ≥four (i.e. 25%) of all Cartoon presentations, to ensure reliable estimates [19].

1) Reaction time to fixation of a target area (RTF) represents the time it took to detect visual information in the target area and to execute an eye

movement toward it, and is a measure for the timing of reflexive visuospatial attention orienting.
2) Fixation duration (FD) was calculated as the average time the eyes were in the stimulus' target area, given the maximum presentation time of 10 s per stimulus. FD is a measure for the duration of sustaining visuospatial attention to a stimulus.
3) Gaze fixation area (GFA) was calculated by drawing an ellipse over the area with the highest density of gaze points (i.e., the part of the target area that contained 85% of all gaze coordinates, using principal component analysis [18,20] and was expressed as the average diameter of the fixated area in degrees. GFA depended on stimulus size and represents the accuracy of fixating visuospatial attention on a target.

2.3.4. Longitudinal analysis of VOF

First, we calculated the average performance at baseline and at follow-up and the absolute changes per parameter, separately for the groups with peripheral, central and nonspecific visual pathology. Second, we compared patterns of VOF in the risk groups with the age-related normative references obtained from a control group without visual impairments [21]. We denoted the number of children with VOF parameter values inside and outside the age-based reference limits at both time points. Values inside the 99.7% reference limits were regarded as normal for the children's age; values outside these limits were regarded as abnormal for their age. After two-year follow-up, we denoted the number of children who changed from normal to abnormal for their age (i.e. in whom parameter values changed from inside to outside the age-based reference limits), and who changed from abnormal to normal (i.e. in whom parameter values changed from outside to inside the age-based reference limits).

3. Results

Table 1 presents clinical information of the children at baseline. In the group aged 1–6 years, children with central pathology more often had clinical CVI (Pearson Chi-square test; $\chi^2 = 6.78$, $p = .034$, adjusted residual = 2.0) than the other groups. In the group aged 7–12 years, children with central pathology more often had clinical CVI ($\chi^2 = 14.31$, $p = .001$, adjusted residual = 3.4) and brain abnormalities on MRI ($\chi^2 = 11.04$, $p = .004$, adjusted residual = 3.2). At the two-year follow-up appointment, the presence of clinical factors had not changed over time and none of the children had had visual interventions. Table 2 shows the results from qualitative VSF assessments (i.e., visual

Table 1
Clinical Factors of the Children with Visual Pathology at Baseline.

Age group: 1–6 years	Peripheral pathology (N = 7)	Central pathology (N = 6)	Nonspecific pathology (N = 4)
Age (mean, *SD*)	5.3 (0.48)	4.9 (1.75)	4.2 (0.73)
Gender (m:v)	5:2 (71% male)	2:4 (33% male)	2:2 (50% male)
Clinical diagnosis of CVI	0 (0%)	4 (67%)*	2 (50%)
Brain abnormalities on MRI	3 (43%)	4 (80%)	1 (25%)
Visual perception problems	2 (29%)	4 (67%)	2 (50%)
Born prematurely	0 (0%)	2 (40%)	0 (0%)
Intellectual level (mean, *SD*)	98 (5)	84 (17)	100 (-)
Intellectual disability	0 (0%)	1 (17%)	0 (0%)
Behavioral disorder	1 (14%)	1 (17%)	0 (0%)
Developmental training	1 (14%)	1 (17%)	2 (50%)
Age group: 7–12 years	**Peripheral pathology (N = 17)**	**Central pathology (N = 23)**	**Nonspecific pathology (N = 7)**
Age (mean, *SD*)	8.9 (1.4)	9.5 (1.7)	8.9 (1.2)
Gender (m:v)	10:7 (59% male)	15:8 (65% male)	6:1 (86% male)
Clinical diagnosis of CVI	1 (6%)	15 (65%)*	3 (43%)
Brain abnormalities on MRI	4 (24%)	14 (61%)*	0 (0%)
Visual perception problems	5 (29%)	13 (57%)	4 (47%)
Born prematurely	2 (12%)	4 (17%)	0 (0%)
Intellectual level (mean, *SD*)	88 (15)	84 (11)	87 (27)
Intellectual disability	3 (18%)	5 (22%)	4 (57%)
Behavioral disorder	8 (47%)	5 (22%)	2 (29%)
Developmental training	7 (41%)	8 (35%)	0 (0%)

Note. Results are shown separately for the two age groups and for the children with peripheral, central, and nonspecific pathology. * = significant differences between this group and the other pathology groups (Chi-square tests).

sensory and oculomotor dysfunctions), measured at baseline. The presence of dysfunctions did not significantly differ between any of the groups. However, strabismus and visual field restrictions were more prevalent in children with central than with peripheral pathology. After two years, changes in the qualitative VSF abnormalities were minimal, did not differ between groups, and are therefore not reported.

3.1. Visual sensory functions (VSF)

Table 3 shows results of the quantitative VSF assessments (i.e. visual acuity and contrast sensitivity) at baseline and follow-up. Children with central pathology had highest mean visual acuity and children with peripheral pathology lowest visual acuity, both at baseline and follow-up. In the group aged 1–6 years, abnormal visual acuity ranged from 33% to 57% at baseline, and was highest in the peripheral group. These percentages increased over two years for most types of visual pathology. Contrast sensitivity values were highest (i.e. worse) in the central group at baseline, whereas at follow-up this was the case for the peripheral group. The number of abnormal contrast scores ranged from 14% to 33% at baseline and these percentages remained or decreased over 2 years. In the group aged 7–12 years, visual acuity was highest in the central and nonspecific group. Abnormal visual acuity rates ranged from 29% to 71% and were highest in the peripheral group, both at baseline and follow-up. Highest contrast sensitivity values and the highest rate of abnormal contrast scores were found in the peripheral group, both at baseline and follow-up. Overall in this age group, higher rates of abnormal contrast scores were found compared to the younger group. These group differences were often based on small group sizes and did not reach statistical significance.

Overall, visual acuity at baseline positively correlated with visual acuity at follow-up ($r_s = 0.79$, $p < .001$), but this was not found for contrast. In children aged 1–6 years, visual acuity and contrast values did not significantly change over two years. However, contrast sensitivity values became lower (i.e. better) in all groups. At 7–12 years, visual acuity values did not change over time, whereas contrast sensitivity values became significantly better in the peripheral and central group (Wilcoxon Signed-Ranks tests: $Z = -2.56$, $p = .011$ and $Z = -2.38$, $p = .017$). In addition, regardless of pathology, a significant negative correlation was found between baseline values and changes over two years for contrast sensitivity ($r_s = -0.81$, $p < .001$). Two-year changes in VSF compared to norm values, i.e. the rate of abnormal scores, are shown in Fig. 2, separately for the two age groups and the different visual pathology groups. In the group aged 1–6 years, the rates of abnormal visual acuity did not change much over 2 years, except for changes to abnormal acuity in about 15% of children with peripheral and central pathology. Contrast sensitivity deteriorated (changed to abnormal) in 14% and 33% of children with peripheral and nonspecific pathology, but improved (changed to normal) in 14% and 33% of children in the peripheral and central group, respectively. In the group aged 7–12 years the rates of abnormal visual acuity did not change much over 2 years, except for changes to abnormal acuity in 14% of children with nonspecific pathology. Contrast sensitivity changed to normal in 12–29% of children (except the nonspecific group), and changed to abnormal in 9–14% of children (except the peripheral group). These differences were not statistically significant, as they were based on low numbers of children who had two-year changes.

3.2. Visuospatial orienting functions (VOF)

Fig. 3 shows the average VOF parameter values of all children in the risk groups compared to the age-related normative reference limits at baseline (left panels), and after two-year follow-up (right panels), separately for RTF (upper panels), GFA (middle panels) and FD (lower panels). Results are shown separately for the three visual pathology groups. Table 4 presents the average values and the percentage of children with abnormal VOF parameter scores for their age (i.e., outside the age-based reference limits) at baseline and at follow-up. The specific amount of children with abnormal VOF depended on the age group and the type of visual pathology. In the group aged 1–6 years, no significant differences in VOF values were found between the clinical groups. In the group aged 7–12 years, significant differences in GFA at follow-up were found between groups (Kruskal-Wallis test: $\chi^2 = 7.68$, $p = .022$). More specific, GFA at follow-up was significantly larger in the peripheral than in the central group ($U = 100$, $z = -2.62$, $p = .009$, Bonferroni-corrected).

In the group aged 1–6 years, the rate of abnormal RTF scores ranged from 43 to 67% at baseline and from 57 to 100% at follow-up. Abnormal RTF was most prevalent in the central group at baseline, but at follow-up no clear group differences were found. The rate of abnormal GFA scores ranged from 67 to 86% at baseline and from 50 to 100% at follow-up and was most prevalent in the peripheral (86%) and nonspecific group (100%). Abnormal FD ranged from 14 to 100% at baseline and from 33 to 50% at follow-up, and was less prevalent in the peripheral than in the other groups. In the group aged 7–12 years, the rate of abnormal RTF scores ranged from 57 to 61% at baseline and 74–86% at follow-up, without clear differences between pathology groups. In the peripheral group, RTF values became significantly faster over two years (median RTF −24 ms; Wilcoxon Signed-Rank test: $z = -2.06$, $p = .039$). The rate of abnormal GFA scores ranged from 71 to 77%

Table 2
Results from Qualitative Visual Sensory and Oculomotor (VSF) Assessments at Baseline.

Age group 1–6 years	Peripheral pathology (N = 7)	Central pathology (N = 6)	Nonspecific pathology (N = 4)
Strabismus	3 (43%)	5 (83%)	1 (25%)
Esotropia	2	3	–
Exotropia	1	2	1
Nystagmus	5 (71%)	5 (83%)	2 (50%)
Manifest	4	3	2
Latent	–	2	–
Manifest + latent component	1	–	–
Ocular motility dysfunction	0 (0%)	1 (17%)	1 (25%)
Visual field restriction	2 (29%)	3 (50%)	2 (50%)
Concentric	1	–	1
Left or right	–	2	–
Upper or lower	1	1	1
Quadrant/hemianopia	–	–	–
Not (reliably) assessed	–	–	–
Stereovision dysfunction	3 (43%)	4 (67%)	1 (25%)
Not (reliably) assessed	–	1	2
Color vision dysfunction	0 (0%)	3 (50%)	1 (25%)
Not (reliably) assessed	–	–	2
Age group 7–12 years	**Peripheral pathology (N = 17)**	**Central pathology (N = 23)**	**Nonspecific pathology (N = 7)**
Strabismus	9 (53%)	15 (65%)	3 (43%)
Esotropia	8	3	2
Exotropia	1	12	1
Nystagmus	14 (82%)	13 (59%)	2 (29%)
Manifest	10	7	1
Latent	3	4	1
Manifest + latent component	1	2	0
Ocular motility dysfunction	4 (24%)	1 (4%)	1 (14%)
Visual field restriction	5 (29%)	8 (35%)	3 (43%)
Concentric	5	3	–
Left or right	–	2	3
Upper or lower	–	1	–
Quadrant/hemianopia	–	2	–
Not (reliably) assessed	–	1	1
Stereovision dysfunction	13 (76%)	12 (52%)	3 (43%)
Not (reliably) assessed	1	–	1
Color vision dysfunction	2 (12%)	2 (9%)	0 (0%)
Not (reliably) assessed	2	2	1

Note. Results are shown separately for the two age groups and for the children with peripheral, central, and nonspecific pathology. Factors that were part of the VSF protocol but that were not present in our sample were not included in this table (e.g. hyper/hypotropia, tunnel vision). The number of children in which a function could not reliably be assessed is indicated for visual field, stereovision and color vision.

at baseline and from 57 to 94% at follow-up, and was most prevalent in the peripheral group. Abnormal FD ranged from 39 to 80% at baseline, with the lowest prevalence in the central group. Abnormal FD ranged from 50 to 57% at follow-up without clear group differences. In the peripheral group, FD values became significantly longer over two years (median FD +546 ms; Wilcoxon Signed-Rank test: $z = -2.05$, $p = .041$).

Fig. 4 shows the number of children who changed from normal to abnormal VOF scores for their age, or vice versa, over the course of two years. Overall, the VOF parameter scores changed more often than their VSF counterparts, and RTF and FD changed more often than GFA. Regardless of age and clinical group, VOF parameters values at baseline significantly correlated with those at follow-up (RTF: $r_s = 0.55$, $p < .001$; GFA: $r_s = 0.51$, $p < .001$; FD: $r_s = 0.40$, $p < .001$). In the group aged 1–6 years, RTF most often changed to abnormal in the peripheral (43%) and nonspecific group (50%). Changes to normal RTF were found in the peripheral (29%) and central (17%) group. GFA changed to abnormal in 14% and 25% of children with peripheral or nonspecific pathology, and changed to normal in 14–33% of children, except for the nonspecific group. FD changed to abnormal most often in the nonspecific group (50%), and only changed to normal in the central group (20%). In the group aged 7–12 years, high rates of changes to abnormal RTF were found in all

Table 3
Results of Quantitative VSF Assesments (Visual Acuity and Contrast Sensitivity) at Baseline and Follow-up.

Age group 1–6 years	Peripheral pathology (N = 7)	Central pathology (N = 6)	Nonspecific pathology (N = 4)
VSF values			
Visual acuity (mean, SD)			
Baseline	0.26 (0.17)	0.40 (0.24)	0.26 (0.35)
Follow-up	0.26 (0.14)	0.36 (0.26)	0.43 (0.35)
Contrast sensitivity (mean, SD)			
Baseline	2.4% (2.8)	5.6% (9.5)	2.5% (1.8)
Follow-up	1.8% (0.7)	1.5% (0.5)	1.6% (2.4)
N abnormal scores			
Visual acuity			
Baseline	4 (57%)	2 (33%)	2 (50%)
Follow-up	5 (71%)	3 (50%)	1 (25%)
Contrast sensitivity			
Baseline	1 (14%)	2 (33%)	1 (25%)
Follow-up	1 (14%)	0 (0%)	1 (25%)
Age group 7–12 years	**Peripheral pathology (N = 17)**	**Central pathology (N = 23)**	**Nonspecific pathology (N = 7)**
VSF values			
Visual acuity (mean, SD)			
Baseline	0.26 (0.17)	0.35 (0.20)	0.39 (0.22)
Follow-up	0.26 (0.19)	0.37 (0.21)	0.39 (0.32)
Contrast sensitivity (mean, SD)			
Baseline	4.4% (5.9)	4.2% (5.3)	2.1% (1.5)
Follow-up	1.9% (2.3)**	1.5% (1.3)**	1.2% (0.7)
N abnormal scores			
Visual acuity			
Baseline	12 (71%)	10 (44%)	2 (29%)
Follow-up	11 (65%)	7 (30%)	3 (43%)
Contrast sensitivity			
Baseline	7 (41%)	8 (35%)	1 (14%)
Follow-up	2 (12%)	7 (30%)	2 (29%)

Note. Results are shown as absolute values (mean, SD), and number (%) of abnormal scores compared to norm values. Visual acuity: higher value = better acuity. Contrast sensitivity: lower value = better contrast. ** = sign difference between baseline and follow-up scores in this group (Wilcoxon signed-rank test).

clinical groups (29–35%), whereas changes to normal RTF were only found in the peripheral and central group (12% and 17%, respectively). GFA was more stable, with changes to abnormal in the peripheral and central group 18% and 9%) and changes to normal GFA in all but the peripheral group (14–22%). Changes to abnormal FD ranged from 29 to 35% but were not seen in the peripheral group, whereas all groups showed changes to normal FD (17–33%).

Finally, in the group aged 7–12 years, significant negative correlations were found between baseline values and changes over two years for RTF ($r_s = -0.56$, $p < .001$), GFA ($r_s = -0.36$, $p = .014$) and FD ($r_s = -0.44$, $p = .003$). After specifying pathology group, the correlations for GFA remained significant only in the peripheral and central group, those for RTF in the peripheral group, and for FD in the central group.

3.3. Associations between VSF and VOF

In addition to outlining the performance and changes in VSF and VOF separately, we also looked at the associations between the two types of visual functioning. In the group aged 1–6 years, GFA changes had a significant negative correlation with contrast sensitivity at baseline ($r_s = -0.51$, $p = .042$). This correlation was found separately in the groups with peripheral and central pathology, although not significant. In the group aged 7–12 years, no significant correlations between VSF and VOF or their two-year changes were found.

Lastly, because the classification for the clinical groups was quite general, Table A3 shows the percentage of VOF abnormalities for the different specific visual impairments resulting from the pathology. In the peripheral group, many children with opticus or optic nerve pathology changed to abnormal RTF and FD.

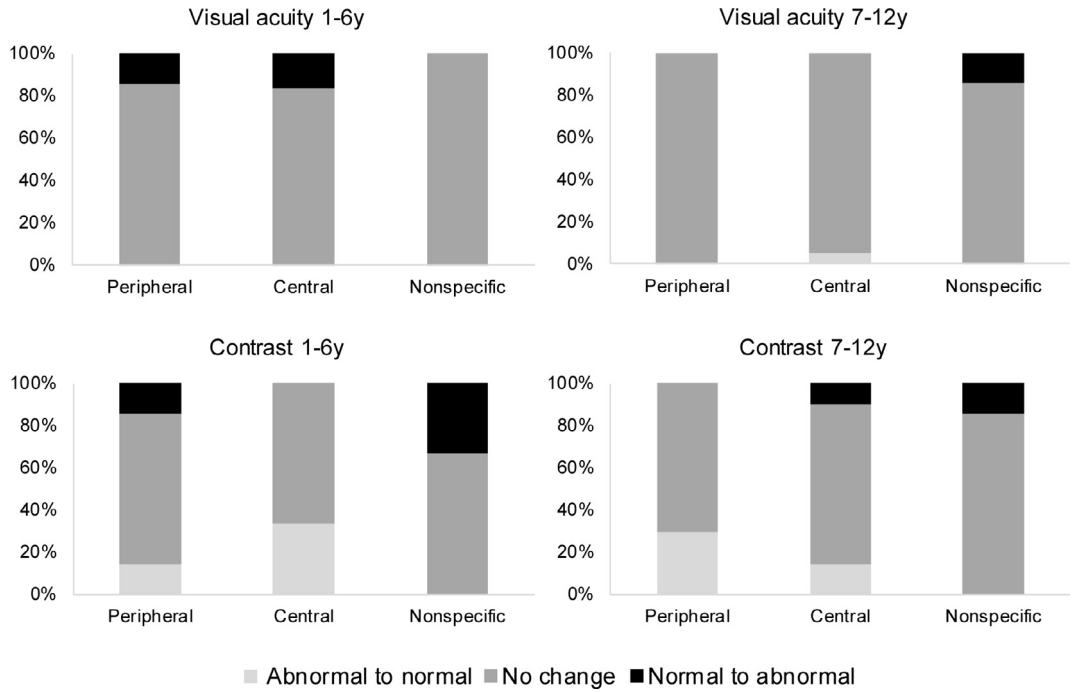

Fig. 2. The number of children who showed changes in quantitative VSF assessments (visual acuity and contrast sensitivity) over the course of two years, separately for children aged 1–6 years (left panels) and aged 7–12 years (right panels). Colors indicate the type of change over time: changed from abnormal to normal (light gray), no change, i.e. stable performance (dark gray), or changed from normal to abnormal (black).

A relatively high percentage of children with albinism and congenital cataract changed to abnormal RTF, whereas all children with congenital cataract changed to abnormal GFA. Within the central group, the type of visual pathology was not related to specific changes.

4. Discussion

In this two-year longitudinal study we quantitatively assessed and followed visual sensory functions (VSF), and visuospatial attention orienting functions (VOF) in a population-based cohort of children (aged 1–6 years and 7–12 years) with visual impairments that were caused by various types of visual pathology. As hypothesized, qualitatively assessed VSF differed between these clinical groups but were relatively constant over two years in most children. For the two quantitatively assessed VSF, visual acuity differences depended on visual pathology, whereas contrast sensitivity showed more changes over time. VOF (measured with eye tracking) were characterized by longer reaction time, shorter fixation duration, and lower fixation accuracy than normal for their age in the majority of children with visual pathology, and particularly orienting reaction times and fixation duration were susceptible to spontaneous changes over two years. The findings should be interpreted in light of the fact that our cohort consisted of visually impaired children, who were clients of a visual advisory center who often had multiple visual and comorbid problems. Between the clinical groups, different patterns of changes in VSF and VOF were found that partly depended on age. The finding that both methods provided distinct and complementary information about visual functioning argues in favor of their combined use in children.

4.1. Following visual performance in children over time by means of VSF & VOF

Although the assessment of a broad spectrum of visual functions and functional visual abilities in children has been advocated [15], longitudinal studies in children with visual disorders are still largely restricted to visual acuity and contrast sensitivity. A few specific studies that reported relatively good prognoses in terms of visual acuity were conducted in children with optic neuritis [8,9], retinopathy of prematurity (ROP) after treatment [10,11], and uveitis after treatment [12]. On the other hand, less visual improvement over time and lower visual acuity outcomes were found in children with perinatal asphyxia [13], or structural brain lesions, meningitis, and encephalopathy [14]. In children with diagnoses of CVI, visual acuity improved over time (i.e. on average two to six years) but remained abnormal in most children [22–24]. This range of followed VSF is limited, and does not always reflect the level of functional visual abilities (i.e. how the child uses its visual abilities [25]). However, in young children it is inevitable

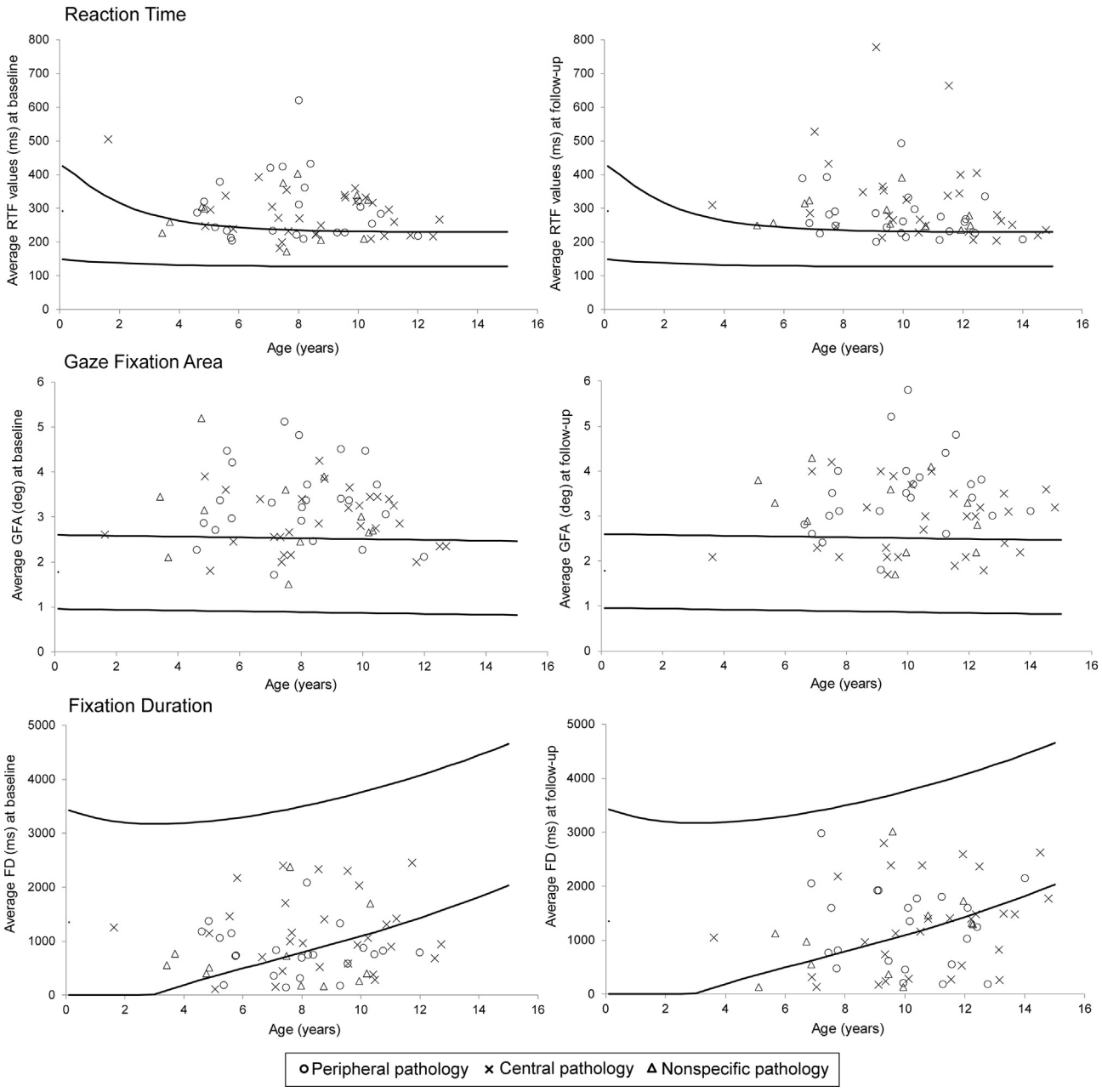

Fig. 3. Upper panels show average RTF in ms, middle panels show average GFA in degrees, and the lower panels show average FD in ms for children in the clinical group plotted against age. Left panels represent results at baseline, right panels represent results after two-year follow-up. Black lines represent the upper and lower age-related 99.7% reference limit, fitted on age. Markers indicate the three pathology groups: peripheral (circles), central (crosses), and nonspecific (triangles).

since there are not many other quantitative VSF assessments available. Therefore, in the current study, we took a broader perspective on following visual functioning.

Firstly, we assessed additional functions in a qualitative manner to get a more comprehensive overview of VSF, for example visual fields and stereovision. To enable performance comparisons in our diverse cohort, these VSF were classified on a binary scale (normal versus abnormal). Therefore, these final results are merely indicative of general patterns in this population, which may in future samples help to predict the individual functioning and changes within specific children over time.

Secondly, we added eye tracking-based, quantitative parameters of visuospatial attention orienting functions. The current PL paradigm entails relatively straightforward, reflexive shifts of eye movements to salient visual information in the near visual environment, and resembles the fixation-shift [26], or pro-saccade paradigm [27]. These relatively simple visual behaviors are indices for

Table 4
Visual Orienting Functions (VOF) Values and Percentage of Abnormal Values, at Baseline and After Two-Year Follow-Up.

Age group 1–6 y	Peripheral pathology (N = 7)	Central pathology (N = 6)	Nonspecific pathology (N = 4)
VOF values (median, IQR)			
RTF			
Baseline (ms)	242 (211–318)	316 (246–421)	280 (235–303)
Follow-up (ms)	279 (248–387)	329 (275–456)	286 (251 (3 2 1)
GFA			
Baseline (°)	2.95 (2.7–4.2)	3.00 (2.29–3.68)	3.30 (2.36–4.76)
Follow-up (°)	3.00 (2.6–3.5)	2.75 (2.10–4.05)	3.55 (3.00–4.18)
FD			
Baseline (ms)	1049 (716–1166)	1201 (561–1639)	530 (432–717)
Follow-up (ms)	1199 (690–2276)	961 (226–1619)	770 (239–1087)
N (%) abnormal values			
Abnormal RTF			
Baseline	3 (43%)	4 (67%)	2 (50%)
Follow-up	4 (57%)	4 (67%)	4 (100%)
Abnormal GFA			
Baseline	6 (86%)	4 (67%)	3 (75%)
Follow-up	6 (86%)	3 (50%)	4 (100%)
Abnormal FD			
Baseline	1 (14%)	2 (33%)	0 (0%)
Follow-up	2 (29%)	2 (33%)	2 (50%)

Age group 7–12 y	Peripheral pathology (N = 17)	Central pathology (N = 23)	Nonspecific pathology (N = 7)
VOF values (median, IQR)			
RTF			
Baseline (ms)	282 (226–389)	266 (219–319)	324 (206–375)
Follow-up (ms)	258 (219–290)**	267 (230–353)	255 (248–296)
GFA			
Baseline (°)	3.35 (2.68–4.08)	2.85 (2.35–3.40)	2.70 (2.45–3.60)
Follow-up (°)	3.70 (3.10–4.20)*	3.00 (2.10–3.50)*	2.80 (2.20–3.60)
FD			
Baseline (ms)	744 (350–828)	994 (590–1712)	405 (182–1704)
Follow-up (ms)	1290 (467–1790)**	1396 (538–2373)	1317 (376–1726)
N (%) abnormal values			
Abnormal RTF			
Baseline	10 (59%)	14 (61%)	4 (57%)
Follow-up	14 (82%)	17 (74%)	6 (86%)
Abnormal GFA			
Baseline	13 (77%)	17 (74%)	5 (71%)
Follow-up	16 (94%)	14 (61%)	4 (57%)
Abnormal FD			
Baseline	12 (71%)	9 (39%)	4 (57%)
Follow-up	8 (47%)	13 (57%)	4 (57%)

Note. RTF = reaction time to fixation; GFA = gaze fixation area; FD = fixation duration. Percentages reflect the number of children with abnormal VOF parameters: i.e. with values outside normative limits at baseline and at follow-up. * = significantly different values between these groups (Kruskal Wallis followed by Mann-Whitney U-tests, $p < .017$). ** significantly different value at follow-up compared to baseline in this group (Wilcoxon Signed-Rank test, $p < .05$).

more complex neurocognitive skills and their development in children [28]. Delayed orienting reaction times are thought to reflect the immaturity or dysfunction of several processes, such as disengaging visual attention from a previous target, shifting visual attention to a new target, or translating sensory to motor coordinates [29]. Hence, the delayed RTFs signal a decreased visuospatial 'vigilance' and concurrently, delayed detection of visual information. Abnormal fixation accuracy indicates difficulties with fixating the eyes on visual details and problems with oculomotor control. Given that active control of fixation has been found to continuously improve during adolescence [30], additional changes may occur after the present age limits (>12 years). Fixation duration, or sustaining the focus of overt visual attention on a stimulus, was abnormal in about 50% of children, and this percentage increased over time in the central and nonspecific group. However, FD literature is contradictory: a longer FD may indicate improvement in sustaining visual attention [31], while

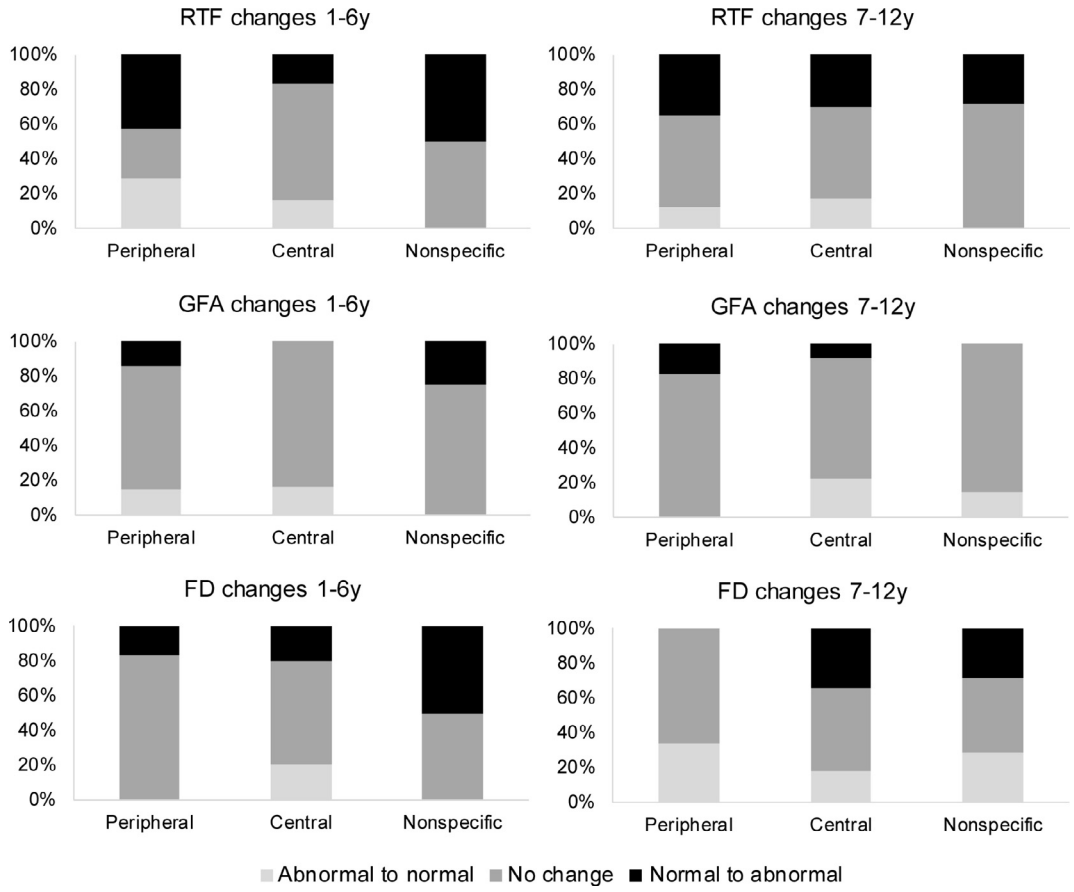

Fig. 4. The number of children who showed changes in VOF parameters (RTF, GFA, FD) over the course of two years, separately for children aged 1–6 years (left panels) and aged 7–12 years (right panels). Colors indicate the type of change over time: changed from abnormal to normal (light gray), no change, i.e. stable performance (dark gray), or changed from normal to abnormal (black).

a shorter FD with age may indicate faster shifts of visuospatial orienting and speed of visual processing [32]. Within the present paradigm, given that the normative developmental FD trajectories increased with age, longer FD over time is assumed to represent normal developmental change. When interpreting two-year changes, intra-individual variability in VOF parameters should be taken into account. This variability has been reported to be ~80 ms for RTF and 0.65 degrees for GFA in visually impaired children [19]. Hence, on an individual level, two-year differences that are larger than these variability levels represent true time-related changes.

4.2. VSF & VOF in children with different types of visual pathology

4.2.1. Children with peripheral visual pathology

A relatively large number of children with peripheral pathology showed changes to abnormal visual acuity at 1–6 years, and larger and more abnormal GFA values at 7–12 years than other groups. Therefore, children in this group would benefit from assessing VSF and VOF from a young age onward. The majority of children in this group had accompanying nystagmus (as measured with the VSF assessment), which may explain their robust deviant fixation accuracy [5,6]. The disorder congenital nystagmus has mainly been related to central dysfunctions, even though its underlying mechanisms are not fully understood [33,34]. Therefore we classified congenital nystagmus as a central disorder.

Delays in visual orienting reaction times have been reported before in adults with optic nerve disorders [35], but not in children with peripheral visual problems. In previous studies in children, optic atrophy was accompanied by a CVI diagnosis [24,36]. In the present study, only one child with peripheral visual pathology had a clinical diagnosis of CVI, indicating visual problems that could not be attributed to ocular pathology alone. Moreover, seven children with peripheral pathology had MRI abnormalities, which may be related to the delayed RTF in this group. Other studies also reported MRI abnormalities in disorders of the peripheral system [37,38], and a combined presence of neurological and ophthalmologic deficits in children [24,36,39]. This indicates that even in children with

'simpler' peripheral visual disorders, detected or undetected brain damage can be an underlying risk factor for abnormal VOF. Given the increasing prevalence of neurological abnormalities in children in general (e.g., due to preterm birth, hypo or hyperoxia), these functional attentional impairments are important to recognize and be aware of in clinical practice, also in ophthalmologic settings.

4.2.2. Children with central visual pathology

Children with central pathology showed higher and more abnormal RTF than other groups at 1–6 years, and higher FD combined with more changes to abnormal FD at 7–12 years. Delayed orienting reaction times are a consistent finding in children with cerebral visual damage and/or CVI [5,6]. In the present study significant delays compared to other pathology types were only found at 1–6 years. At 7–12 years however, children in this group did not show improved RTF after two years, opposed to children with peripheral and nonspecific pathology. The fact that this abnormal VOF remained abnormal, may indicate chronic visuospatial orienting problems in the children with central pathology. In particular these RTF findings argue for early VOF screening in children with (risks of) central pathology. In some children, prolonged reaction times may be related to the higher prevalence of accompanying visual field restrictions in this group. The persistent delays in RTF were not related to a specific type of central pathology. This finding is in line with a previous longitudinal study that failed to find a clear relation between the type of brain damage and visual function recovery over time [22].

Similar to the present results, RTF to highly salient visual stimuli has never been found to correlate with visual acuity in children [6], indicating two separate processes or functions. With regard to the broad concept of CVI it is evident that a CVI diagnosis alone does not clarify the functional problems experienced by a child [40,41]. The presented VOF parameters may provide a new and much-wanted measure of functional visual behavior and its prognosis in children with brain damage-related (i.e. central) visual impairments or CVI.

4.2.3. Children with nonspecific visual pathology

The rationale to include children without demonstrable visual system pathology but with evident visual impairments was to provide functional information on visual performance in this group. Of the 11 children, five had a clinical diagnosis of CVI that most likely was a diagnosis 'by exclusion' of peripheral lesions [40]. The onset of CVI was classified as nonspecific, or idiopathic, in 17% of children with clinical CVI, opposed to a previous report of 9.4% [24]. At a young age (i.e., 1–6 years), their rate of VOF and VSF abnormalities resembled that of children with central pathology, whereas in older children (7–12 years) no clear resemblance with a type of pathology was found. This seems plausible, given that at a young age peripheral disorders are easier to assess and rule out than central visual problems. Based on VOF, however, a risk for central visual problems may become evident at an earlier age than currently possible in this population.

4.3. Extending visual assessments with VOF tasks

An important application of measuring VOF on an individual level concerns the field of visual diagnostics. The assessment and interpretation of pediatric vision tests can be challenged by a lack of visual attention in children, but also by factors such as crowding (problems with discriminating visual objects in cluttered surroundings). These factors can be identified and accounted for by examining VOF patterns. The presented patterns were generated in the context of a PL task, but they may generalize to overall visual functioning: if visual attention allocation to stimuli in the visual environment is slower, less accurate, or very brief, this may impair the degree to which the visual information enters the peripheral and central visual system. Consequently, abnormal VOF might affect concurrent processing and perception of visual information. However, the degree to which delayed orienting speed in general translates to, for example, impaired detection of optotypes in VSF tests or of visual information in the child's daily environment, is yet unknown and requires further investigation.

Although VOF abnormalities can be noticed in children's behavior during conventional visual assessments, they are not easy to distinguish in detail by a human observer alone. With the present eye tracking-based method, specific patterns of VOF were assessed nonverbally and with a simple visual stimulus. Such eye tracking-based paradigms are easily administered, relatively fast to perform (from 5 min testing time), and provide highly accurate recordings with a low percentage of data loss (i.e., 14% of the included children in our study). This means that this tool may also be used to evaluate other patient populations who can be difficult to assess but are at risk of complex visuospatial attention or processing problems (e.g., with neurocognitive disabilities or poorly understood visual complaints). Having more functional information available may guide daily support and interventions in such high-risk groups.

As outlined in our discussion of the three types of visual pathology, the nature of the visual pathology may determine functional consequences and opportunities for spontaneous changes in VSF or VOF. For example, differential patterns were found between peripheral and central pathology. Furthermore, the fact that some children showed normalization of VOF while at the same time they showed deterioration of VSF over time,

and vice versa, emphasizes that both assessments add unique information to classifying a child's visual performance. Extending conventional VSF assessments with automated VOF assessments can provide a more comprehensive overview and monitoring of children's visual functioning than assessing VSF alone. In addition, it may lead to designing attentional and viewing strategies that may be beneficial in daily situations. Besides managing expectations based on the type of pathology, looking at individual longitudinal patterns of VSF and functional VOF may benefit the clinical and practical approach to children.

5. Study limitations

In the current study we presented a two-year follow-up of visual functioning in a visually impaired population. Especially in the group aged 1–6 years, sample size was low, which has influenced our results and their significance. This was partly caused by heterogeneity of visual pathology in our group, and by the lower admission rate of younger children to visual rehabilitation practices. The conclusions should therefore be verified in larger samples. Ideally, all children with visual pathology are followed from infancy onwards to study differential developmental trajectories. With regard to VOF, high variability was found in the younger children, both with and without visual impairments. Such variance rates seem inevitable and have even been reported in more homogeneous groups of children, e.g. with visual acuity measures [23]. Naturally, the prevalence of abnormal VOF results depended on the width of the normative reference limits. More liberal limits (e.g. corresponding with 95% intervals instead of the current 99.7%) would have resulted in an even higher prevalence of abnormal VOF in the visual pathology groups. Normally, visual acuity and contrast sensitivity scores are comparable, but in the present study contrast sensitivity was less often abnormal than visual acuity. This was caused by the fact that some examiners took into account visual acuity performance when scoring contrast sensitivity performance. Therefore, the absolute VSF scores may provide a more objective view than the normal-abnormal classification.

In general in longitudinal studies, possible systematic bias comes from learning effects, environmental noise, and inter-observer variability. We minimized these influences by using reflexive measures, the same examiners in each year, and automated analyses with strict criteria. Lastly, although in this study we relied on the assumption that the localization of eye movements corresponds with the locus of visuospatial attention, it is known that these do not always overlap [42]. However, in the context of the present simple, reflexive PL paradigm and the population of relatively young children, we believe the VOF parameters are good indicators of visuospatial attention orienting. Questions that remain are if and how this individual visual functioning changes after longer follow-up and after visual intervention programs.

Acknowledgements

The authors are grateful to the children and their parents for participation in this longitudinal study. The authors thank the following orthoptists and optometrists from Royal Dutch Visio for performing the majority of visual function (VSF) assessments for this study: Sandra van der Zwet Slotenmaker, Nadine Naumann, Heleen Schreuders, Frederiek te Voortwis, Shantal Torregrosa, Yvonne Flerig, Marlien Kruiswijk, Mariette van der Splinter, Birgit Limonard and Fieneke Allema. The authors thank the coordinators and the directors of the schools for special education and the regional centers of Royal Dutch Visio where this study was conducted. We are grateful to Dr. Lena Jacobson for consultation about classifying the groups based on visual pathology, and to Stephanie van de Langkruis for her help in data analysis.

Declaration of Conflicting Interests

The authors declare that there is no conflict of interest.

Funding

Financial support for this research was provided by ZonMW InZicht (Dutch Organization for Health Research and Development - Insight society), grant number: 60-00635-98-10. The funding source had no involvement in design, data collection, analysis and interpretation, writing of the report and the decision to submit the article for publication.

Ethical approval

This study was approved by the medical ethical committee of the Erasmus Medical Center (MEC 2012-097).

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.braindev.2018.09.006.

References

[1] Sonksen PM, Dale N. Visual impairment in infancy: impact on neurodevelopmental and neurobiological processes. Dev Med Child Neurol 2002;44:782–91.
[2] Daw NW. Visual development, Vol. 9. New York: Springer; 2006.
[3] Teller DY. The forced-choice preferential looking procedure: a psychophysical technique for use with human infants. Infant Behav Dev 1979;2:135–53.

[4] Kooiker MJ, van der Steen J, Pel JJ. Development of salience-driven and visually-guided eye movement responses. J Vision 2016;16:18.
[5] Pel J, van der Does L, Boot F, et al. Effects of visual processing and congenital nystagmus on visually guided ocular motor behaviour. Dev Med Child Neurol 2011;53:344–9.
[6] Kooiker MJ, Pel JJ, van der Steen J. The relationship between visual orienting responses and clinical characteristics in children attending special education for the visually impaired. J Child Neurol 2015;30:690–7.
[7] Boot FH, Pel JJM, Evenhuis HM, van der Steen J. Factors related to impaired visual orienting behavior in children with intellectual disabilities. Res Dev Disabil 2012;33:1670–6.
[8] Brady KM, Brar AS, Lee AG, Coats DK, Paysse EA, Steinkuller PG. Optic neuritis in children: clinical features and visual outcome. J AAPOS 1999;3:98–103.
[9] Morales DS, Siatkowski RM, Howard CW, Warman R. Optic neuritis in children. J AAPOS 1999;37:254–9.
[10] Wu WC, Lin RI, Shih CP, et al. Visual acuity, optical components, and macular abnormalities in patients with a history of retinopathy of prematurity. Ophthalmology 2012;119:1907–16.
[11] Early Treatment for Retinopathy of Prematurity Cooperative Group. Final visual acuity results in the early treatment for retinopathy of prematurity study. Arch Ophthalmol 2010;128:663.
[12] Kump LI, Castañeda RAC, Androudi SN, Reed GF, Foster CS. Visual outcomes in children with juvenile idiopathic arthritis–associated uveitis. Ophthalmology 2006;113:1874–7.
[13] McCulloch DL, Taylor MJ, Whyte HE. Visual evoked potentials and visual prognosis following perinatal asphyxia. Arch Ophthalmol 1991;109:229–33.
[14] Clarke MP, Mitchell KW, Gibson M. The prognostic value of flash visual evoked potentials in the assessment of non-ocular visual impairment in infancy. Eye 1997;11:398–402.
[15] Atkinson J, Anker S, Rae S, Hughes C, Braddick O. A test battery of child development for examining functional vision (ABCDEFV). Strabismus 2002;10:245–69.
[16] WHO. International statistical classification of diseases and related health problems. World Health Organization; 2004.
[17] van Genderen M, Dekker M, Pilon F, Bals I. Diagnosing cerebral visual impairment in children with good visual acuity. Strabismus 2012;20:78–83.
[18] Pel JJM, Manders JCW, van der Steen J. Assessment of visual orienting behaviour in young children using remote eye tracking: methodology and reliability. J Neurosci Meth 2010;189:252–6.
[19] Kooiker MJ, van der Steen J, Pel JJ. Reliability of visual orienting response measures in children with and without visual impairments. J Neurosci Meth 2014;233:54–62.
[20] Oliveira LF, Simpson DM, Nadal J. Calculation of area of stabilometric signals using principal component analysis. Physiol Meas 1996;17:305.
[21] Kooiker MJ, Pel van der JJ, Steen-Kant SP, van der Steen J. A method to quantify visual information processing in children using eye tracking. J Vis Exp 2016;113.
[22] Watson T, Orel-Bixler D, Haegerstrom-Portnoy G. Longitudinal quantitative assessment of vision function in children with cortical visual impairment. Optometry Vision Sci 2007;84:471–80.
[23] Lim M, Soul JS, Hansen RM, Mayer DL, Moskowitz A, Fulton AB. Development of visual acuity in children with cerebral visual impairment. Arch Ophthalmol 2005;123:1215–20.
[24] Huo R, Burden SK, Hoyt CS, Good WV. Chronic cortical visual impairment in children: aetiology, prognosis, and associated neurological deficits. Brit J Ophthalmol 1999;83:670–5.
[25] Colenbrander A. Towards the development of a classification of vision related functioning. In: Dutton GN, Bax M, editors. Visual impairment in children due to damage to the brain. London, UK: MacKeith Press; 2010. p. 282–94.
[26] Atkinson J, Hood B, Braddick OJ, Wattam-Bell J. Infants control of fixation shifts with single and competing targets-mechanisms of shifting attention. Perception 1988;1988(17):367–8.
[27] Westheimer G. Mechanism of saccadic eye movements. AMA Arch Ophthalmol 1954;52:710–24.
[28] Ross-Sheehy S, Perone S, Macek KL, Eschman B. Visual orienting and attention deficits in 5-and 10-month-old preterm infants. Infant Behav Dev 2017;46:80–90.
[29] Salman MS, Sharpe JA, Eizenman M, et al. Saccades in children. Vision Res 2006;46:1432–9.
[30] Luna B, Velanova K, Geier CF. Development of eye-movement control. Brain. Cognition 2008;68:293–308.
[31] Aring E, Grönlund MA, Hellström A, Ygge J. Visual fixation development in children. Graef Arch Clin Exp 2007;245:1659–65.
[32] Shaddy DJ, Colombo J. Developmental changes in infant attention to dynamic and static stimuli. Infancy 2004;5:355–65.
[33] Abadi RV. Mechanisms underlying nystagmus. J Roy Soc Med 2002;95:231–4.
[34] Papageorgiou E, McLean RJ, Gottlob I. Nystagmus in childhood. Pediatr Neonatol 2014;55:341–51.
[35] Trope GE, Eizenman M, Coyle E. Eye movement perimetry in glaucoma. Can J Ophthalmology 1989;24:197–9.
[36] Khetpal V, Donahue SP. Cortical visual impairment: etiology, associated findings, and prognosis in a tertiary care setting. J AAPOS 2007;11:235–9.
[37] Waugh MC, Chong WK, Sonksen P. Neuroimaging in children with congenital disorders of the peripheral visual system. Dev Med Child Neurol 1998;40:812–9.
[38] Grönqvist S, Flodmark O, Tornqvist K, Edlund G, Hellström A. Association between visual impairment and functional and morphological cerebral abnormalities in full-term children. Acta Ophthalmol Scan 2001;79:140–6.
[39] Dale N, Sakkalou E, O'Reilly M, Springall C, De Haan M, Salt A. Functional vision and cognition in infants with congenital disorders of the peripheral visual system. Dev Med Child Neurol 2017;59:725–31.
[40] Boot FH, Pel JJM, van der Steen J, Evenhuis HM. Cerebral visual impairment: which perceptive visual dysfunctions can be expected in children with brain damage? A systematic review. Res Dev Disabil 2010;31:1149–59.
[41] Ortibus E, Lagae L, Casteels I, Demaerel P, Stiers P. Assessment of cerebral visual impairment with the L94 visual perceptual battery: clinical value and correlation with MRI findings. Dev Med Child Neurol 2009;51:209–17.
[42] Posner MI. Orienting of attention. Q J Exp Psychol 1980;32:3–25.