Early identification of cerebral visual impairments in infants born extremely preterm

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AIM Children born extremely preterm are at risk of visual processing problems related to brain damage. Damage in visual pathways can remain undetected by conventional magnetic resonance imaging (MRI) and functional consequences cannot always be predicted. The aim of this study was to assess the efficacy of processing visual information in infants born extremely preterm at a corrected age of 1 year using a communication-free visual function test based on eye tracking.

METHOD Infants born extremely preterm (<29wks' gestation) without apparent white and grey matter damage on conventional MRI at 30 weeks' postmenstrual age were included (19 males, 1.01y [0.96–1.24] (median [25th–75th centiles]); 11 females, 0.99y [0.98–1.01]). At the corrected age of 1 year, reaction times to fixation (RTF) of specific visual properties displayed on an eye-tracker monitor were quantified and compared with results from a comparison group (eight males, 1.28y [1.01–1.33]; nine females, 1.10y [0.90–1.20]).

RESULTS The infants in the preterm group had longer response times in detecting colour patterns (red–green) and motion compared with infants in the comparison group. No impairments were detected in oculomotor functions (saccades, pursuit, and fixations).

INTERPRETATION The data suggest that delays in processing visual information can be identified in children born extremely preterm. The delays might be ascribed to deficits in neuronal connectivity in visual pathways at a microstructural level.

With increasing numbers of preterm births and increasing survival rates,[1] there is a growing recognition that a substantial number of infants born preterm will develop long-term neurodevelopmental problems related to cognitive and neurosensory performance.[2] Encephalopathy of prematurity includes various lesions, such as periventricular leukomalacia, which is often the result of hypoxia-ischemia and affects white matter around the lateral ventricles.[3,4] Periventricular leukomalacia can typically cause damage to the optic radiations, the axon bundles that convey visual information from the lateral geniculate nucleus to the primary visual cortex.[5] It has become evident that periventricular leukomalacia is often accompanied by axonal or neuronal disease, which leads to a decrease of volume of neuronal structures such as the thalamus, basal ganglia, cerebellum, and cerebral cortex.[4,6] It has been reported that neonates with damage in these brain areas have a high risk of visual sensory dysfunctions between the age of 0 years and 14 years, such as low visual acuity, reduced visual fields, and oculomotor problems.[7–11] In addition, children born preterm also form a high-risk group for cerebral visual impairments.[12] Between 6 years and 16 years of age, impaired sensory and perceptual visual functions are often found in children born preterm.[13–16]

In many cases, neurodevelopmental and visual processing problems can be the result of brain injuries associated with preterm birth, such as venous infarctions, that are detectable using conventional magnetic resonance imaging (MRI). However, these problems might also be the result of deficits in neuronal connectivity in optic tracts at the microstructural level.[4] The problem is that these deficits remain undetected by conventional MRI. In addition, the location of lesions does not always predict the resulting functional impairments. Consequently, detection of visual processing impairments within the first critical years calls for a more specific and functional approach. In the present study, we presented visual stimuli with one or multiple specific visual modalities (colour, form, and motion) on a monitor with an integrated eye-tracking device.[17] We designed a method to measure reflexive eye movements in combination with a preferential looking paradigm, based on a young child's preference to look at patterned surfaces over homogeneous ones.[18] Because this does not require verbal communication with a child, infants with and

without visual processing deficits can be measured from 6 months onwards.[17] With this method, ocular motor control parameters such as pursuit, reflex saccades, and fixations are determined, as well as the efficacy of processing visual information in terms of response times. Previously, we showed that responses to high-contrast and slowly oscillating cartoons are delayed in children with a clinical diagnosis of cerebral visual impairments.[19] Processing of such visual stimuli requires the capability of integrating various visual modalities (colour, form, motion, contrast) into a visual percept. It was suggested that children with cerebral visual impairments may have difficulty with the simultaneous integration of these separately processed visual modalities.

The aim of this study was to test for visual processing deficits in infants born extremely preterm without structural brain injury on conventional MRI at 30 weeks postmenstrual age. Their processing speed in terms of response times of specific visual modalities was assessed at a corrected age of 1 year and compared with that of term born infants at the age of 1 year. Our hypothesis was that response times were delayed in infants born extremely preterm.

METHOD
Participants
Between May 2010 and January 2013, infants born below 29 weeks gestational age were recruited prospectively as part of a single centre neuroimaging study. Standard clinical neuroimaging included serial cranial ultrasonography from birth until discharge and MRI at 30 weeks postmenstrual age (29 4/7–30 4/7wks). Of the 336 eligible infants, 29 were excluded because of congenital malformation (n=18), uncertainty regarding gestational age (n=5), or refusal of parental informed consent (n=6). Of these infants, 122 had an MRI at 30 weeks (the others were either scanned later or had no scan because of an unstable clinical condition or death). Twenty patients had severe brain injury, so 102 infants were eligible for this study. Twenty-two patients were lost to follow-up.

In February 2012, recruitment of 1-year-old infants through their parents started for this eye-tracker study (n=42). From February 2012 till January 2013, the parents of 30 infants (19 males and 11 females, median gestational age at birth 27.6wks [26.3–28.1wks, 25th–75th centiles]) gave informed consent for participation and publication of the results (inclusion rate of 71.4%). MRIs were independently assessed by a neonatologist (>10y of MRI research experience) and a paediatric neuroradiologist (>20y of experience). Preterm infants with no apparent white matter and grey matter damage were included—this is 'the preterm group'. Exceptions were made for small germinal matrix haemorrhages (grade I according to Papile et al.[20]), and small punctuate cerebellar haemorrhages (see Fig. S1, 'Supplementary methods', online supporting information, for the MRI protocol). All patients with other lesions were excluded. Other exclusion criteria were visual acuity

What this paper adds
- Children born extremely preterm are at risk of delays in processing visual information.
- Children born extremely preterm may have deficits in visual pathways at a microstructural level.
- Visual processing problems seem to be associated with preterm birth.
- Visual deficits can be assessed with a visual function test based on eye tracking.

<0.15 (Snellen equivalents; this was tested using a 4.8cycles/cm Teller card at 55cm viewing distance) and retinopathy of prematurity (>3) assessed by a paediatric ophthalmologist. All infants performed the visual test at 1 year corrected age (see Table I for additional demographic data). Seventeen infants born at term and tested with all visual stimuli at an age between 0.65 years and 1.35 years (eight males and nine females) were selected from a comparison database. This database contained measurements of 300 children between 1 year and 12 years of age. These children were recruited from day care centres and primary schools between 2010 and 2014. The children in this database had no history of prematurity or other risk factors for brain injury or visual deficits —this is 'the comparison group'. Only those children were selected who were assessed with the selected visual stimuli for this study.

Measurement set-up and procedures
The set-up consisted of a 24-inch monitor with an integrated infrared eye-tracking system sampling at 60Hz (Tobii T60 XL; Tobii Corporation, Danderyd, Sweden), which measured gaze position of each eye separately using cornea reflection of infrared light (latency ±30ms) and compensated for head movements in a certain range. Each child sat on the lap of the parent or day care supervisor or in a pram at approximately 60cm distance from the monitor to ensure efficient tracking. The experiments were conducted in a quiet room with ambient light conditions. Five different stimuli were presented to trigger visual processing of different aspects of visual information combined (Fig. S1a) or in isolation (Fig. S1b,c,d,e). The target area of each stimulus was presented in one of four quadrants of the monitor (according to the concept of preferential looking). The cartoon stimulus contained several visual modalities, such as colour, contrast, form, and motion. The other stimuli were designed to trigger a single modality of visual processing (colour pattern [red–green], form coherence, motion detection, or motion coherence). Two sequences of stimuli were presented on the eye-tracker monitor using Tobii Studio (Tobii Corporation). Each block/sequence contained visual stimuli that were presented multiple times in a randomized order. The cartoon stimulus was presented 16 times in each sequence with a presentation time of 8 seconds, all other stimuli were presented four times in each sequence with a presentation time of 4 seconds. Cartoons were shown more often to maintain a child's attention towards the monitor.

Table I: Gestational age and age at visual test of the children in the preterm and comparison group (median [25th–75th centiles])

Study group	n	Sex	Age at visual test	Gestational age
Preterm	19	Male	1.01y [0.96–1.24]	27.6wks [26.6–28.0]
	11	Female	0.99y [0.98–1.01]	26.9wks [26.2–27.9]
Comparison	8	Male	1.28y [1.01–1.33]	–
	9	Female	1.10y [0.90–1.20]	–

In addition to these stimuli, basic ocular motor functions were tested by showing alternating (saccades) and moving (pursuit) white smileys (with a diameter of 3° visual angle and moving with a velocity of 4° per second in a 16° horizontal and vertical sinusoidal motion across the monitor). A 5-point calibration procedure was performed before stimulus presentation. In cases where this procedure was unsuccessful, for example because of lack of visual attention or incomplete capturing of gaze, the experimenter conducted a post calibration before analysis. In this procedure, gaze data related to cartoon stimuli were plotted and rescaled to their known locations. All measurements were stored on hard disk.

Data analysis and statistics
Reflex eye movement data were analysed off-line using self-written Matlab programs (Mathworks Inc., Natick, MA, USA). To analyse orienting responses, gaze data were recalculated as a visual angle between gaze location and centre of the stimuli using the average viewing distance per child. For each target area a circular area of interest was defined with a radius of 6° for cartoon, colour, and motion detection stimuli. Because the target area for form and motion expansion stimuli was slightly larger, we set the area of interest for these stimuli to 8°. The centre of the area of interest corresponded with the centre of the target area of each stimulus. Gaze data were quantified in terms of reaction time to fixation (RTF), which was defined as the time from presentation of a stimulus until gaze reached its area of interest. RTF represented efficiency of processing visual information followed by an ocular motor response. At least one successful orienting response (gaze entered the target area) per participant per stimulus type was required for further processing of the data (see Fig. S1, 'Supplementary methods').

Per stimulus type and study group, the RTF values were not normally distributed (Kolmogorov–Smirnov test; $p>0.05$). Consequently, we used non-parametric tests for data analysis. Differences in RTF values between the study groups were analysed using the Mann–Whitney U test. When a group comparison revealed a statistically significant difference for a visual stimulus, a cluster analysis was done on the RTF values of both groups. The aim was to identify two clusters based on the RTF values of that particular visual stimulus. This test identified the number of infants in both the comparison and preterm groups who responded relatively fast and those who responded relatively slow. In all tests, a p-value <0.05 was considered to

be statistically significant. All statistical analyses were performed using SPSS 21.0 (SPSS Inc., Chicago, IL, USA).

The experimental procedures were approved by the medical ethical committee of Erasmus University Medical Center, Rotterdam, the Netherlands (MEC-2012-097). The study adhered to the Declaration of Helsinki for research involving human participants.

RESULTS
Visual inspection of gaze data revealed no impairments in saccade and pursuit oculomotor performance. Table I summarizes information per study group. No significant between-group differences were found for (corrected) age at the time of the measurements (males: median [25th–75th centiles], 1.01y [0.96–1.24] in the preterm group versus 1.28y [1.01–1.33] in the comparison group; U=40.5, p=0.058; females: 0.99y [0.98–1.01] in the preterm group versus 1.10y [0.90–1.20] in the comparison group; U=32.0, p=0.180). All infants succeeded in at least two of the five tasks (e.g. making orienting responses to at least two types of visual stimuli), 91% succeeded in at least three tasks, 85% in at least four tasks, and 49% succeeded in all five tasks. Table II shows the number of infants who successfully fixated the different stimulus types per study group. These success rates were lower for infants in the preterm group, except for the stimulus cartoon (100% in both groups). This success rate was lowest for the colour stimulus in both groups.

Figure 1 shows box-whisker plots of the RTF values for the comparison and the preterm groups per stimulus type. Table III presents the median and 25th–75th centiles of the RTF values obtained per stimulus type per study group. At 1 year corrected age, the infants in the preterm group showed significantly higher RTFs for the colour stimulus (1950ms [1645–2435] and 1240ms [790–1405]

Table II: Number of children who successfully fixed the stimuli with five different visual modalities

Visual stimuli	Comparison group, n=17 (%)	Preterm group, n=30 (%)
Cartoon	17 (100)	30 (100)
Colour	9 (53)	11 (37)
Form	16 (94)	21 (70)
Motion detection	17 (100)	25 (83)
Motion expansion	14 (82)	16 (53)

Data are shown per stimulus type per study group and include percentages relative to group size.
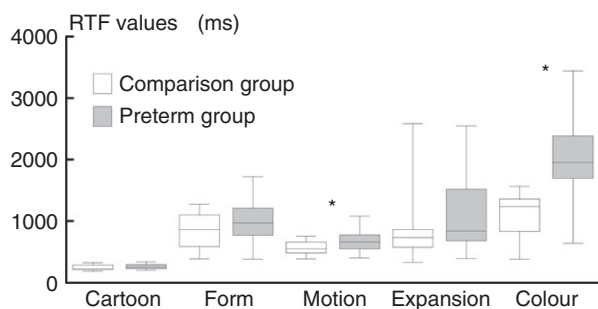
Figure 1: Box-whisker plots of the reaction time to fixation (RTF) values obtained in infants in the comparison and the preterm groups per visual stimulus type. The asterisks indicate significantly higher RTF values for the preterm group compared with the comparison group. The RTF vales are presented in milliseconds (ms).

respectively, U=13.0, $p<0.05$) and the motion detection stimulus (660ms [550–790] and 550ms [480–670] respectively, U=143.0, $p<0.05$) compared with infants in the comparison group. Although significant on a group level, not all infants in the preterm group had delayed responses. By applying a clustering test, we counted in the cluster with relatively slow RTF values for motion detection 12 of the 25 (48%) infants of the preterm group and 4 of the 17 (24%) infants of the comparison group for motion detection. For colour, we counted 9 of the 11 (82%) infants in the preterm group and one of the nine infants in the comparison group in the cluster with relatively slow RTF values.

DISCUSSION
Preterm birth can have a large impact on typical brain development and on visual processing functions in particular. In the present study, we determined the efficacy of processing visual information in terms of an RTF in a group of infants born extremely preterm. On a group level we showed delayed response times for motion and colour related stimuli at a corrected age of 1 year. This delay in visual processing was present despite the absence of ophthalmological damage or visible brain damage evaluated with conventional MRI. Although significant on a group level, not all infants born extremely preterm showed delayed responses to either motion or colour related stimuli. In 48% of the tested infants born extremely preterm, we found delayed responses to at least one of the tested

visual modalities at 1 year corrected age. Our next step is to follow the development of visual processing in this group and to relate early visual information processing to other aspects of child development, such as motor, cognitive, social, and emotional development.

Our results are consistent with previously published data on impairments in motion processing in children born preterm between 6 years and 16 years of age.[14–16] Our data suggest that processing motion related stimuli is already impaired at age 1 year. Previously published data on colour dysfunction did not reveal any dysfunction in a group of adolescents who were born extremely preterm and/or with an extremely low birthweight.[21,22] In these studies, the presence of a colour deficiency was tested with Ishihara colour plates that score colour vision performance on a non-continuous scale (seen or unseen). However, in the present study, it was not our primary goal to assess the presence of a colour deficiency, but to assess delays in the processing of different modalities. Thus, the response time gives information on the integrity of the colour processing in the visual pathway anywhere between the first processing steps in the retina up to the central processing of visual information where visual input is decomposed into motion, colour, form, and contrast. In the present preterm group, we found delayed response times to this colour stimulus during the first year of life. Note that the percentage of infants in which a response time was obtained was relatively small in both the preterm and the comparison groups (53% and 37% respectively). We cannot rule out the possibility that some of the infants (in the comparison as well as the preterm groups) were colourblind. As 8% of males have impaired red-green photoreceptor processing deficits, this could have caused the lack of response. An alternative explanation is that the colour patterns were not visually salient enough for 1-year olds, resulting in the low percentages reported.

The test results provide quantitative information on reflexive bottom-up processing of visual information. Note that this method does not give information on perceptual aspects of visual processing. During the processing of a visual stimulus, a further integration step is needed to bind the various visual modalities into a stable percept. Delayed responses to one or more modalities assessed on an individual level could be of help to identify possible affected brain areas. Theoretically, it could even be that the conversion of visual information into an oculomotor signal is impaired. It is highly unlikely that this was the case in the present preterm group. The oculomotor responses to the

Table III: Reaction time to fixation (RTF) to stimuli with five different visual modalities of the children in the preterm and comparison group (median [25th–75th] centiles)

Study group	Cartoon, ms	Colour, ms	Form, ms	Mot. detection, ms	Mot. expansion, ms
Preterm	260 [230–290]	1950 [1645–2435]	975 [750–1235]	660 [550–790]	840 [670–1600]
Comparison	220 [210–290]	1240 [790–1405]	865 [560–1110]	550 [480–670]	735 [560–900]

See Table II for the number of successfully obtained RTF values per study group. RTF values are presented in milliseconds (ms) for five different stimuli: Cartoon, Colour, Form, Motion (Mot.) detection and Motion expansion.

cartoon stimulus in this group, which triggered the fastest responses, were not significantly different from those assessed in the comparison group. This suggests that the specific delays found in the present preterm group for colour and motion detection are the result of the first steps of processing this information rather than the final steps of oculomotor preparation and execution.

A first study limitation was that not all stimuli provoked an orienting response. This was not caused by the eyes not being tracked properly by the eye-tracker system, because we had RTF values for the cartoon stimulus in all infants. As stated, we found a low number of responses in both the preterm and the comparison groups for the colour stimulus (53% and 37% respectively). Except for colour, the percentages were comparable with those previously reported in a large group of children from 1 year to 12 years of age attending special education for the visually impaired.[19] A second study limitation was that we did not have as many infants in the comparison group as in the preterm group. We recruited comparison participants between 1 year and 4 years of age at day care centres for two different studies. Thus, although more children around the age of 1 year were present in our database, not each infant was assessed with the selected visual stimuli for this study.

The data presented in this study argue in favour of using this approach to identify children at risk of long-term visual disorders. Note that this group had no visible brain damage evaluated from conventional MRI. However, more detailed imaging techniques such as diffusion tensor imaging are emerging. Diffusion tensor imaging is a good and reliable tool to assess microstructural differences in white matter caused by both maturation and damage that are not visible on conventional MRI sequences.[23] One of our goals is to use diffusion tensor imaging in combination with data obtained from eye tracking measurements to study the relationship between early neonatal white matter damage and later visual outcome. It has already been shown that low visual acuity is related to damage to early visual pathways such as the optic radiation and the corpus callosum.[7,10,11,14] Recent studies have shown the facility to visualize and quantify the ventral and dorsal stream in children and adults from 6 years onwards using diffusion tensor imaging.[24,25] This gives the opportunity to relate structure to function in both early, and extrastriate visual pathways. This could facilitate working towards early intervention programmes and parenting programmes for children with cerebral visual impairments.

CONCLUSION

In 48% of the tested children born extremely preterm, we found delayed responses to at least one of the tested visual modalities at 1 year corrected age, which suggests higher order visual processing problems. Because these children had no ophthalmological impairments or structural brain damage on conventional MRI, the data suggest deficits in neuronal connectivity in visual pathways at a microstructural level.

ACKNOWLEDGEMENTS

SUPPORTING INFORMATION

The following additional material may be found online:

Figure S1: Includes cartoon (A), colour (B), form (C), motion detection (D), and motion coherence (E) stimuli (the red arrows represent the motion of the stimulus), as well as 'Supplementary methods'.

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