Pediatric RESEARCH

CLINICAL RESEARCH ARTICLE

Early visuospatial attention and processing and related neurodevelopmental outcome at 2 years in children born very preterm

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BACKGROUND: The ability to perceive and process visuospatial information is a condition for broader neurodevelopment. We examined the association of early visuospatial attention and processing with later neurodevelopmental outcome in very preterm infants.

METHODS: Visuospatial attention and processing was assessed in 209 children (<30 weeks gestation) using an easy applicable eye tracking-based paradigm at 1 and 2 years. Average reaction times to fixation (RTF) on specific visual stimuli were calculated, representing time needed for overall attention (Cartoon stimuli) and processing (Motion and Form stimuli). Associations between RTFs and various measures of development at 2 years including cognitive and motor development (Bayley Scales of Infant and Toddler Development-Third edition; Bayley-III), language (Lexi test) and behavior (Child Behavior Checklist) were examined.

RESULTS: At 1 year, 100 ms slower Cartoon and Motion RTFs were associated with lower cognitive Bayley-III scores (−4.4 points, 95%CI: −7.4; −1.5 and −1.0 points, −1.8; −0.2, respectively). A 100 ms slower Cartoon RTF was associated with a 3.5 (−6.6; −0.5) point decrease in motor Bayley-III score.

CONCLUSIONS: Visuospatial attention and motion processing at 1 year is predictive of overall cognitive and motor development 1 year later. The nonverbal eye tracking-based test can assist in early detection of preterm children at risk of adverse neurodevelopment.

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IMPACT:

- Visuospatial attention and processing at 1 year corrected age is predictive for overall cognitive and motor development 1 year later in preterm infants.
- First study to relate early visuospatial attention and processing with later neurodevelopmental outcome in preterm children.
- Early detection of preterm children at risk of adverse neurodevelopment, which allows for more timely interventions.

INTRODUCTION

Children born very preterm (gestational age < 32 weeks) have an increased risk of neurodevelopmental impairment, which often presents in early childhood and lasts into adolescence and adulthood, as reflected by learning disabilities at school or work.[1–5] Early detection of probable neurodevelopmental impairment allows for timely interventions and individualized follow-up trajectories to prevent further delay. Standard neonatal follow-up programs mostly include preterm infants based on gestational age (GA, generally below 30 or 32 weeks) and/or birth weight (below 1000 or 1500 g).[6,7] In this approach, not all children at risk of neurodevelopmental impairment are reached (e.g. children at risk but outside follow-up criteria), while redundant follow-up may take place in those who develop well. Current neurodevelopmental testing methods in young children are often lengthy (and thus demanding for the child) and costly (due to the need of trained personnel), and have limited predictive value for later IQ performance if used at an early age.[8,9] Therefore, there is a need for quick and easy tests, which have a reliable predictive value that can be performed from an early age.

Neurodevelopmental impairment can be reflected in a broad spectrum of motor, cognitive, language, sensory and perceptual or behavioral problems.[10–13] An important conditional factor for both cognitive and motor development is visual (spatial) function, namely the ability to attend, perceive and process visual and spatial information in the environment.[14] Visuospatial attention

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and processing are vital functions that develop early in life and are regulated by an extensive cerebral network.[15] Visuospatial dysfunction is prevalent in preterm children, both with and without evident damage on brain imaging.[14,16–20] A recent cross-sectional study has linked delayed visual processing to impaired academic achievement in adolescents born extremely preterm.[21] As a result, they recommended testing of visual processing at a younger age: essential both to maximize early support and to study the predictive value of visual processing for later cognitive development.

Visual fixation (to a target moving horizontally, vertically and in an arc) has been tested at birth in full-term infants[22] and gaze gain (visual tracking through horizontal smooth pursuit, head movements and saccades) at 4 months in preterm infants.[23] Both measures showed a positive association with neurodevelopment at 2, 3 and/or 5 years. This suggests that early visuospatial testing could be predictive of later child development. Recently, a quantitative eye tracking-based method was developed to nonverbally assess visuospatial attention and processing.[24–26] During this assessment, a child is presented with specific visual stimuli on a computer screen, while simultaneously eye movements are recorded using an integrated eye tracker. This way, reflexive viewing reactions to visual stimuli are quantified using reaction time and accuracy. This method can reliably detect abnormalities in visuospatial attention and various visual processing functions in children born very preterm at 1 year.[18,27] While "normal" development of visuospatial attention and processing is reflected by a significant decrease in viewing reaction times over age,[26] viewing reaction times do not always catch up with this normative developmental trajectory in infants born preterm, resulting in a high prevalence of visuospatial delays at 1 and 2 years.[18,20,27] It is not yet known whether visuospatial attention and processing at 1 or 2 years, assessed using this eye tracking-based method, is associated with other neurodevelopmental domains.

In this study we hypothesized that delayed visuospatial attention and processing function at 1 and 2 years is related to neurodevelopmental impairment, and that these visuospatial functions can be used as early predictors of overall impaired neurodevelopment in children born very preterm. More specifically, the aims of this study are:

(1) to explore a possible association between visuospatial attention and processing at 1 and 2 years, and cognitive and motor development, expressive language and behavioral problems at 2 years; and
(2) if an association is present, to evaluate whether there is added value in using these early measures of visuospatial attention and processing function for predicting neurodevelopmental outcome at 2 years compared to a prediction based on neonatal risk factors.

METHODS

Subjects

All preterm infants with a gestational age between 24 and 30 weeks who were admitted to the Neonatal Intensive Care Unit (NICU) of the Erasmus MCSophia Children's Hospital in Rotterdam within 48 h after birth between 2011 and 2017 and who participated in the Blik Vooruit Study (Study A)[27] and/or the BOND Study (Study B)[28] were eligible for this study ($n = 283$). Combining these two cohorts was deemed suitable based on large similarity in source population, inclusion criteria, goals, methods and data collected.[27,28]

Infants were excluded from the study because of severe congenital or chromosomal abnormalities, perinatal asphyxia (cord blood/first postnatal PH < 7.0 and APGAR score at 5 min < 5), an intraventricular hemorrhage (IVH, on cranial ultrasound in neonatal period) of grade III (with/without infarction), post-hemorrhagic ventricular dilation (PHVD) requiring lumbar punctures, congenital TORCHES infection (toxoplasmosis, rubella, cytomegalovirus, herpes simplex, and other organisms including syphilis, parvovirus and varicella zoster) and those without any visuospatial assessment at 1 and 2 years CA. We also excluded children with retinopathy of prematurity (ROP, as assessed by a pediatric ophthalmologist) grade III or higher who received ophthalmic treatment (peripheral retinal laser photo-ablation or intravitreal bevacizumab injection) based on the association with impaired visual function which could influence eye tracking results.[29] In this study age refers to age corrected for prematurity.

Parental informed consent was obtained for all participants. Both Study A and Study B were approved by the medical ethical committee of the Erasmus Medical Center, Rotterdam.

Neonatal risk factors

Patient data were collected retrospectively (Study A) and prospectively (Study B) from the children's electronic medical records and regular follow-up questionnaires. These data consisted of parental characteristics (education level and ethnicity) and basic perinatal factors including antenatal steroids, sex, GA, birth weight, multiplet status, APGAR score and cord blood pH. From the neonatal period, information on respiratory (infant respiratory distress syndrome, bronchopulmonary dysplasia, mechanical ventilation, postnatal steroids), cardiac (inotropics, persistent ductus arteriosus), gastrointestinal (necrotizing enterocolitis, abdominal surgery), infectious (sepsis), neurologic (IVH, periventricular leukomalacia (PVL), stroke, intracerebral bleeding) and ophthalmologic (ROP) factors, as well as data on general ill being (GA at discharge, duration of hospital admission) were explored.

Assessment and analysis of visuospatial attention and processing

All participants underwent visuospatial testing at 1 year and/or 2 years using the eye tracking-based method as previously described in more detail.[18,24,26,27] To guarantee sufficient visibility of the visuospatial assessment, a minimal visual acuity of 0.15 (Snellen equivalents, assessed with 4.8 cycles/cm Teller Acuity Card at 55 cm viewing distance) was ensured prior to the test. During the test the child was seated on the parent's lap at 60 cm distance from a 24-inch monitor with an integrated infrared eye tracking system sampling at 60 Hz (Tobii T60XL; Tobii Corporation, Danderyd, Sweden). The system measures the gaze position of each eye separately with a latency of 30 ms. It also compensates for head movements within a range of 50–80 cm eye-monitor distance. After a standardized five-point calibration, children's viewing reactions were recorded during the presentation of a preferential looking paradigm on the monitor.[30] In the paradigm, various visual stimuli with distinctive target areas were randomly presented and used to assess visuospatial attention orienting and various types of visual processing.[27] To maintain the child's attention to the monitor, a standard set of short audiovisual movie clips was presented in between the test stimuli. During test administration basic oculomotor functions (saccades and smooth pursuit) were evaluated by observation. Total test duration was approximately 8 min. The assessment was repeated a second time in children who were able to maintain concentration.

Recorded eye movement data were analyzed offline using Matlab-based software (Mathworks Inc., Natick MA, USA), with a focus on reflexive, externally triggered viewing reactions to the different visual stimuli (a more detailed description is described previously).[18,27] For each stimulus presentation, it was recorded whether the child detected the stimulus' target area and calculations regarding how fast the eyes reached the target were gathered (average reaction time to fixation, RTF).[25] RTF is a measure for the time needed to process presented visual information and execute an eye movement towards it. We analyzed viewing reactions to three stimuli that were previously found to be delayed in preterm

children at 1 year including: Cartoon (a measure of general visuospatial attention orienting), Motion and Form (measures of motion and form processing).[27] To reach previously reported high reproducibility rates, strict criteria were used for inclusion of RTFs in further analyses (i.e. the child had to detect at least 20% of presentations per stimulus).[25]

For each child, the RTFs of all three stimuli were classified as either normal (within 95% confidence interval) or delayed (above the 95% confidence interval) based on a previously described normative reference sample of age-matched full-term-born controls.[26] Patterns of RTF delays (yes/no) from 1 to 2 years were categorized into four groups per stimulus: children with normal RTF at both ages (normal-stable), children with delayed RTF at both ages (abnormal-stable), children who changed from normal RTF at 1 year to delayed RTF at 2 years (deteriorated) and vice versa (normalized).[20]

Neurodevelopmental assessment

All children were routinely invited to the outpatient clinic at 2 years as part of the national neonatal follow-up program. During this visit, physical and neurological examination was done by a neonatologist or pediatric neurologist. Extensive testing of psychomotor development was performed by a trained physiotherapist and psychologist using the fine motor and gross motor (summarized in a total motor score) and cognitive tests of the Bayley Scales of Infant and Toddler Development-Third edition (Bayley-III, Dutch edition: Bayley-III-NL).[31] In adherence to Dutch guidelines, expressive language development was evaluated by use of the Lexi test; a validated questionnaire completed by parents in order to quantify the child's vocabulary.[32] For each child, parents were asked to complete the Child Behavior Checklist for 1.5–5 years (CBCL); an internationally validated screening tool examining 13 domains of behavioral and emotional problems.[33] Neurodevelopmental outcomes were classified as moderately impaired when test scores were between 70–84 (cognitive and motor Bayley-III), 71–80 (Lexi test) or 60–63 (CBCL), whereas impairment was classified as severe for scores <70, <71 and >63 respectively. The neurodevelopmental assessors as well as the parents were not aware of the child's visuospatial test performance.

Statistical analysis

Statistical analysis was carried out using IBM SPSS Statistics, version 25.0 (IBM SPSS Statistics, Armonk, NY). *P* values (two-tailed) below 0.05 were considered statistically significant. As most of the neonatal factors, neurodevelopmental outcomes and all visuospatial parameters were not normally distributed, medians and interquartile ranges were reported. Nonparametric statistical tests were used to explore selection bias, missing data and group differences.

For the main analyses, linear regression models were used to explore associations between each of the three RTFs (Cartoon, Motion and Form stimuli) at 1 and 2 years and neurodevelopmental outcomes at 2 years. The primary focus was on four outcome measures: the cognitive and total motor scores of the Bayley-III, the total CBCL score and the Lexi score. To restrict multiple testing, additional analyses on the fine and/or gross motor subscales (Bayley-III) or the internalizing and externalizing subscales of the CBCL were conducted only if statistically significant associations were found between RTFs and the total motor and/or total CBCL score. Similarly, only if the RTF of a stimulus at 1 year showed a significant association with a certain outcome, further association of the patterns of delay from 1 to 2 years was explored for that outcome, given that the number of children within the delay pattern subgroup allowed for this. We evaluated effect size (β and adjusted R^2) and significance levels (*P* values) of the models. Subgroup analyses on RTFs and the studied associations were performed in groups of children with or without ROP, with or without brain injury and below or above 28 weeks GA.

To evaluate the predictive value of visuospatial testing for neurodevelopmental outcome, a "basic neonatal" multiple linear regression model was first devised. Out of all neonatal variables available, seven variables with low collinearity were selected based on their relevance reported in literature: sex, GA, combined parental education level, grade of bronchopulmonary dysplasia (BPD; 0: no BPD, 1: mild BPD, 2: severe BPD), treated patent ductus arteriosus (PDA; medical/surgical), brain injury (IVH grade II, stroke, cerebral bleeding or PVL) and duration of hospital admission.[2,34–38]

Firstly, the RTFs that were associated with at least one of the neurodevelopmental outcomes and evaluated their predictive values (R^2) were selected. Secondly, the "basic neonatal" multiple regression model was compared to a model that additionally included the RTFs ("neonatal and visuospatial" model). Using linear hierarchical regression models, the additional predictive value of visuospatial testing was expressed by the increase of predictive capacity (difference in adjusted R^2) by adding the RTFs. All residuals of the linear regression analyses were distributed fairly normally and there were no extreme outliers to exclude from analysis. Correction for multiple testing was not deemed necessary given the step-based and exploratory character of the analyses.

RESULTS

Participants

Figure 1 describes the inclusion of 209 children, with patient characteristics shown in Table 1. Comparisons with excluded children and by original study participation (Study A, Study B or both) only showed differences that mirror our exclusion criteria or the time period of inclusion.

Visuospatial assessment

The visuospatial results for the three stimuli at 1 and 2 years are presented in Table 2, with rates of reliable tests ranging between 77 and 93%. The RTFs generally became faster between 1 and 2 years, as reflected by a decrease in RTFs for the Motion (−177 ms, $P = <0.001$) and Form stimulus (−232 ms, $P = 0.005$). For all three stimuli, 66–69% of children had normal RTFs at both time points. Out of the children with reliable test results at 1 year, 34% showed delayed RTFs for at least one of the three stimuli presented. The prevalence of children with delayed RTFs increased from 16% at 1 year to 23% at 2 years for the Cartoon stimulus and from 12 to 33% ($P = 0.001$) for the Motion stimulus, which translates to around 20% of children with a deteriorating RTF pattern over time. When compared to the total study group, this group did not differ with respect to neonatal risk factors or neurodevelopmental outcome. In contrast, the rate of delayed response to the Form stimulus decreased from 19% at 1 year to 15% at 2 years. Subgroup analyses showed no significant differences in RTFs between children with or without ROP, with or without brain injury or born below or above 28 weeks of gestation.

Neurodevelopmental outcome

Table 3 shows the prevalence of neurological complications such as cerebral palsy and visual disorders (e.g. refractive error, strabismus, nystagmus), as well as median scores on the neurodevelopmental tests. Moderate to severe impairment for cognitive performance, motor functioning, language development and behavioral outcome was found in 8.2, 7.4, 24.1 and 7.3% of children, respectively.

Associations between visuospatial assessment and neurodevelopmental outcome

There were minimal associations between the seven neonatal risk factors and the RTF of any of the three stimuli at 1 or 2 years, although treated PDA and total days of hospital admission were associated with RTF Cartoon at 1 year, and sex with RTF Motion at 2 years, respectively (Supplementary Table S1B).

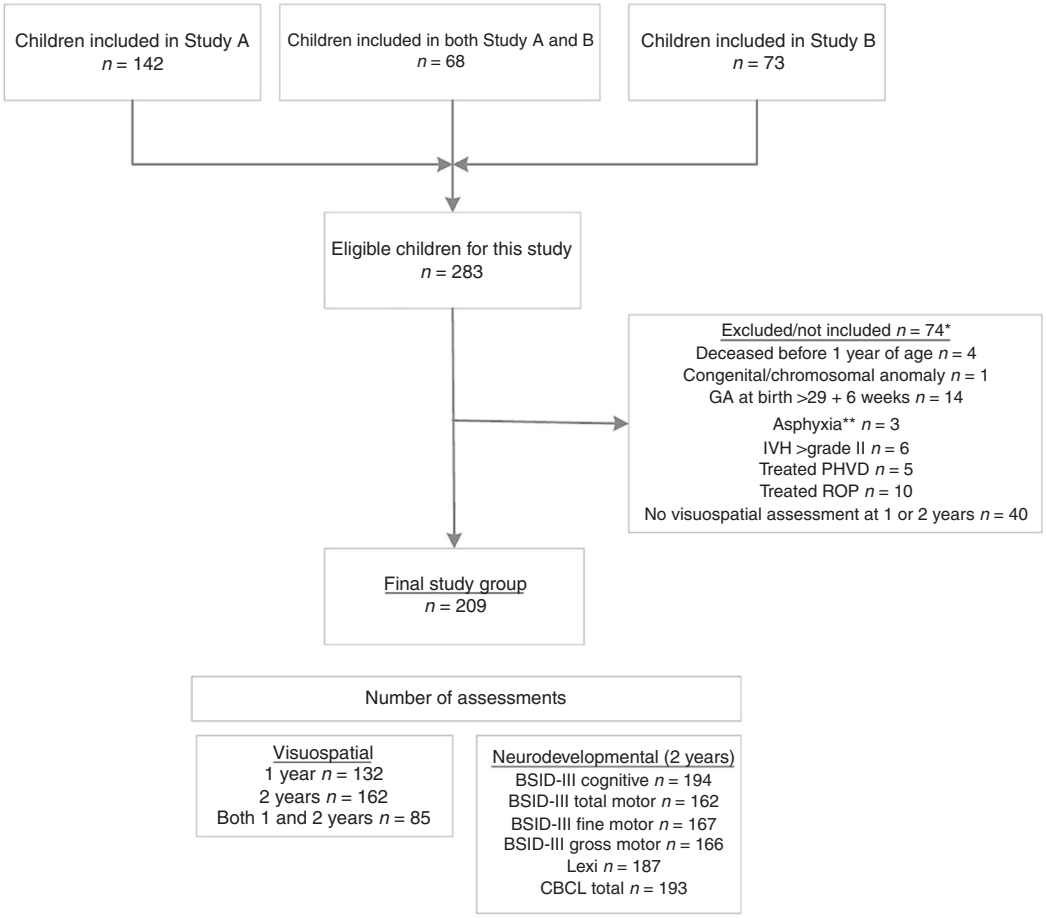

Fig. 1 Flow chart of the study group. *Numbers per reason of exclusion exceed total number of children excluded as some children were excluded for multiple reasons. **Cord blood/first postnatal PH < 7.0 and APGAR score at 5 min < 5. GA gestational age, IVH intraventricular hemorrhage, PHVD Post-Hemorrhagic Ventricular Dilation, ROP retinopathy of prematurity.

The associations between the RTFs of the three stimuli at 1 and 2 years and the four neurodevelopmental outcomes are shown in Table 4. Higher (slower) Cartoon and Motion RTFs at 1 year were significantly associated with a lower cognitive Bayley-III score at 2 years: a 100-ms increase in RTF of the Cartoon stimulus was associated with a 4.4 point (95% CI: −7.4; −1.5) lower cognitive Bayley-III score, whereas a 100-ms increase in Motion RTF resulted in a lowering of cognitive score by 1.0 point (95% CI: −1.8; −0.2). In addition, a 100 ms higher RTF of the Cartoon stimulus at 1 year was associated with a 3.5 (95% CI: −6.6; −0.5) point lower total motor Bayley-III score, which was mainly explained by the gross motor score ($\beta = -0.9$, 95% CI: −1.5; −0.3, $R^2 = 8.2\%$) but not by the fine motor score ($\beta = -0.5$, 95% CI: −1.2; 0.3, $R^2 = 0.6\%$). Subgroup analyses showed that the above significant associations were strongest in children born after 28 weeks GA, without brain injury or without ROP. There were no significant associations for the RTFs of the Form stimulus, nor for any of the RTFs with language and behavioral outcomes. Furthermore, none of the RTFs at 2 years were associated with any of the four outcomes at the same time point.

Results of the exploratory regression analyses on the patterns of delay in Cartoon RTF and cognitive and motor outcome should be interpreted with caution because of the small sample sizes in three of the four pattern-subgroups. There was a trend showing that a normal-stable pattern ($n = 44$) was regularly followed by higher Bayley-III motor scores ($\beta = 8.2$, 95% CI: 1.9; 14.4; median score 107). A normalized pattern ($n = 6$) was linked to lower cognitive scores ($\beta = -5.95$, 95% CI: −15.3; 3.4; median score 96) as well as motor scores ($\beta = -10.87$, 95% CI: −20.6; −1.1; median score 93), when compared to the total study group.

Explanatory value of RTFs compared to neonatal risk factors

The explanatory values (R^2) of RTF of the Cartoon (7.2%) and Motion (4.5%) stimuli for the cognitive Bayley-III outcome were either in a similar range as explanatory values of the individual neonatal risk factors (e.g. 5.6% for BPD grade, 6.7% for total days of hospital admission or 8.9% for parental education), or higher (e.g. R^2 for GA, sex, treated PDA and brain injury were 0.3–1.5%). Similarly, for the motor Bayley-III score, the variance explained by the Cartoon RTF (4.4%) was within the range of variances explained by the individual neonatal risk factors (0.0–8.9%) (Table 4 and Supplementary Table S1A).

In Table 5 we show the effect sizes of the combined "basic neonatal" model and the "neonatal and visuospatial" model. There was a small but significant increase in explained variance of the cognitive Bayley-III score when RTFs of the Cartoon and Motion stimuli at 1 year were added to the "basic neonatal" model ($R^2 = 3.9\%$, $P = 0.04$). Adding the Cartoon and Motion RTFs to the "basic neonatal" models for motor Bayley-III, Lexi or CBCL scores did not increase the effect size of these models.

DISCUSSION

Our study showed that delays in visuospatial attention and motion processing at 1 year CA are associated with lower Bayley-III cognitive and motor scores at 2 years CA. The individual

Table 1. Patient characteristics of the study population.

	Study population ($n = 209$)
Sex (female)	94 (45%)
Multiplet	63 (30%)
GA at birth (weeks)	27.7 [26.6;28.7]
Birth weight (g)	1020 [868;1240]
Umbilical cord PH (mol/l)	7.31 [7.25;7.36], unknown 38 (18%)
Apgar5min (0–10)	8 [6;9], unknown 3 (1%)
Combined parental education level	
Low	29 (14%)
Middle	54 (26%)
High	103 (49%)
Unknown	23 (11%)
Ethnicity by country of birth parents	
Western European	151 (72%)
Non-Western European	50 (24%)
Unknown	8 (4%)
Inotropics	21 (10%)
Treated PDA	78 (37%)
Antenatal steroids	175 (84%), unknown 15 (7%)
IRDS (surfactant)	137 (66%)
Intubation	133 (64%)
Time on mechanical ventilation (days)	2 [0;7], unknown 4 (2%)
Postnatal steroids	38 (18%)
BPD, of which:	63 (30%)
Mild	44 (21%)
Severe	19 (9%)
NEC	10 (5%)
Culture proven sepsis	72 (34%)
IVH, of which:	53 (25%)
Grade I	22 (11%)
Grade II	31 (15%)
PVL	8 (4%)
Stroke	10 (5%)
Cerebellar bleeding	4 (2%)
ROP, of which:	67 (32%)
Grade I	52 (25%)
Grade II	11 (5%)
Grade III	4 (2%)
Surgery[a], for reason:	39 (19%), unknown 1 (1%)
PDA	19 (9%), unknown 1 (1%)
NEC	3 (1%), unknown 1 (1%)
Other abdominal	13 (6%), unknown 1 (1%)
Other general (e.g. hernia inguinalis)	17 (8%), unknown 1 (1%)
Admission NICU (days)	29 [10;54], unknown 1 (1%)
Admission hospital (days)	84 [70;102], unknown 8 (4%)
GA at discharge (weeks)	39.6 [38.0;41.3], unknown 8 (4%)

Data are shown as median [interquartile range] or absolute numbers (percentage).
GA gestational age, *PDA* persistent ductus arteriosus, *BPD* bronchopulmonary dysplasia, *NEC* necrotizing enterocolitis, *IVH* intraventricular hemorrhage, *PVL* periventricular leukomalacia, *ROP* retinopathy of prematurity, *NICU* neonatal intensive care unit.
[a]Numbers per reason of surgery exceed total number of children with surgery as some children had multiple surgeries for varying reasons.

Table 2. Visuospatial attention and processing parameters at 1 and 2 years.

	1 year ($n = 132$)	2 years ($n = 162$)	*P* value
Age at measurement	1.00 [0.99; 1.03]	2.00 [1.99; 2.06]	
Cartoon			
Number of reliable tests	111 (84%)	141 (87%)	
% of stimuli detected	42% [29;58]	54% [33;75]	
Reaction time to fixation (ms)	275 [227;326]	251 [224;289]	0.83
Number delayed compared to term peers	18 (16%)	33 (23%)	0.17
Pattern of delay from 1 to 2 years	($n = 67$)		
Normal-stable	44 (66%)		
Abnormal-stable	4 (6%)		
Deteriorated	13 (19%)		
Normalized	6 (9%)		
Motion			
Number of reliable tests	113 (86%)	151 (93%)	
% of stimuli detected	50% [25;75]	50% [38;84]	
Reaction time to fixation (ms)	710 [571;853]	533 [456;642]	**<0.001**
Number delayed compared to term peers	14 (12%)	50 (33%)	**0.001**
Pattern of delay from 1 to 2 years	($n = 75$)		
Normal-stable	50 (67%)		
Abnormal-stable	6 (8%)		
Deteriorated	17 (23%)		
Normalized	2 (3%)		
Form			
Number of reliable tests	102 (77%)	145 (90%)	
% of stimuli detected	25% [13;50]	50% [25;75]	
Reaction time to fixation (ms)	1037 [810;1388]	805 [623;1016]	**0.005**
Number delayed compared to term peers	19 (19%)	22 (15%)	1.00
Pattern of delay from 1 to 2 years	($n = 58$)		
Normal-stable	40 (69%)		
Abnormal-stable	1 (2%)		
Deteriorated	8 (14%)		
Normalized	9 (16%)		

Count values are shown as absolute numbers (percentage), reaction times to fixation and % of stimuli detected are shown as median [interquartile range]. Reaction time to fixation and number of delayed were compared within the subgroup with measurements at both time points (Wilcoxon signed ranks test and McNemar's test, respectively). Reaction times to fixation, number of delayed and patterns of delay were only calculated for reliable tests. Number and patterns of delay represent comparisons with the normative RTF references. Bold numbers indicate $P < 0.05$. Normal-stable = no delay at 1 or 2 years, Abnormal-stable = delay at both 1 and 2 years, Deteriorated = no delay at 1 year but delay at 2 years; Normalized = delay at 1 year but no delay at 2 years.

Table 3. Neurodevelopmental outcome of the study population at 2 years.

	Study population ($n = 209$)
CP, of which:	11 (5.3%), unknown 1 (0.5%)
GMFCS I	6 (2.9%)
GMFCS II	2 (1.0%)
GMFCS III	1 (0.5%)
GMFCS IV	2 (1.0%)
Visual disorders, of which:	13 (6.2%)
Wearing glasses	10 (4.8%)
Strabismus	6 (2.9%)
Nystagmus	1 (0.5%)
Bayley-III cognitive score, of which:	101 [91;105], unknown 15 (7.2%)
Moderate impairment (score 70–84)	14 (7.2%)
Severe impairment (score < 70)	2 (1.0%)
Bayley-III total motor score, of which:	100 [92;109], unknown 47 (22.5%)
Moderate impairment (score 70–84)	11 (6.8%)
Severe impairment (score < 70)	1 (0.6%)
Bayley-III fine motor score	11 [9;13], unknown 42 (20.1%)
Bayley-III gross motor score	9 [7;10], unknown 43 (20.6%)
Lexi test score, of which:	92 [82;102], unknown 22 (10.5%)
Moderate impairment (score 71–80)	28 (15.0%)
Severe impairment (score < 71)	17 (9.1%)
CBCL total score, of which:	44 [38;53], unknown 16 (7.7%)
Borderline problem behavior (score 60–63)	5 (2.6%)
Clinical problem behavior (score > 63)	9 (4.7%)
CBCL internalizing score	43 [37;51], unknown 16 (7.7%)
CBCL externalizing score	47 [41;55], unknown 16 (7.7%)

Data are shown as median [interquartile range] and absolute numbers (percentage).
CP cerebral palsy, *GMFCS* Gross Motor Function Classification System, *Bayley-III* Bayley Scales of Infant and Toddler Development-Third edition, *CBCL* Child Behavior Checklist.

explanatory values (R^2) of these visuospatial factors (i.e. viewing reaction times to the Cartoon and Motion stimuli) for the cognitive and motor Bayley-III outcome are similar to or higher than explanatory values of known important neonatal risk factors such as sex, gestational age, BPD or parental education in our study. Adding the visuospatial factors at 1 year to a prediction model with a combined set of neonatal risk factors leads to a modest but significant increase in explanatory value for cognitive neurodevelopmental outcome at 2 years.

The proportion of reliable assessments (77–93%) and prevalence of delayed visuospatial attention and processing (12–33%) and a deteriorating delay pattern (20%) in this study are comparable to previous reports in (preterm) children using the same eye tracking-based method at the same ages.[18,20,27,39] However, in the current, larger, study, we found slightly fewer children with delayed RTF for the Cartoon stimulus at 1 year (16%, compared to 19–23% in previous studies).[20,27] This difference may be due to the low rate of severe brain damage in the study group following the exclusion of children with IVH grade III (with or without infarction) and treated PHVD who are more likely to have a complicated neonatal course and impaired neurodevelopmental outcome. Although not all children with severe brain injury were excluded (the cohort still contained some children with stroke, PVL or cerebral bleeding), this may also explain the relatively high neurodevelopmental scores and normal rates of impaired expressive language development and behavioral problems in our study group when compared to previous literature.[40–45]

The strongest association between visuospatial attention and processing function at 1 year and neurodevelopmental outcomes at 2 years was found for visuospatial attention orienting, measured with the highly salient Cartoon stimulus.[26] It seems plausible that the general ability to orient visual attention is closely related to the relatively broad measures of cognitive and motor development. In addition, we found an association between viewing reaction times to the Motion stimulus and cognitive outcome. Reacting to this stimulus requires the detection and processing of movement, which typically starts developing around 3 months of age and is regulated by the so-called *dorsal* visual processing pathway.[14] This dorsal pathway is also involved in attentional capabilities, and is therefore likely to be implicated in viewing reactions to the Cartoon stimulus as well. Disturbance of this *dorsal* pathway can be present irrespective of evidence for brain damage, which suggests compromised cerebral connectivity on a more microstructural level.[18,19] On the other hand, detecting and processing of Form information is regulated by the so-called *ventral* visual processing pathway, which is more often related to periventricular brain damage and starts developing after 4–6 months of age.[14,19] This differential maturation process may translate to the larger intra-individual variation in RTFs for the Form stimulus at early ages in both preterm and full-term-born children.[20,27] This less reliable and discriminative nature of RTF of the Form stimulus may explain why it was not associated with any of the outcomes.

Importantly, the measurement of visuospatial attention and processing as employed in the present study revolves around reflexive viewing reactions to visual input. These reactions are indicative of the efficiency with which visual input is detected, processed, and responded to by means of an eye movement. Given that visuospatial orienting is a relatively low-level function (i.e., *acknowledging* to see something yes/no) with limited cognitive involvement (i.e., it does not involve *understanding* what you see),[46] it is unlikely that delayed viewing reactions are directly related to cognitive dysfunction. Instead, this association may be mediated by top-down or executive attentional functions that are more directly related to general cognitive development. Alternatively, viewing reactions may be a qualitative marker of visual information conduction, in the sense that better-developed cerebral connectivity could allow for faster viewing reactions but also for faster cognitive processing.

Using the eye tracking-based method at 1 year significantly added to the prediction of neurodevelopmental outcome at 2 years. However, the added explanatory value to our "basic neonatal" prediction model was small (R^2 3.9%) and only present for cognitive Bayley-III score. This added value is lower than the 11.4% increase in the predictive ability Kaul et al. found for cognitive Bayley-III outcome at 3 years after adding visual tracking function to their—slightly different—neonatal model.[23] However, direct comparison of these percentages is complicated by important differences in type of visual function tested (i.e. visual tracking of the eyes versus processing functions) and exclusion criteria. Moreover, our well performing "basic neonatal" model for cognitive outcome, with an R^2 of 35%, may have left less room for improvement.

Language and behavioral outcomes at 2 years had no significant relation with visuospatial attention and orienting at 1 or 2 years, and low or even absent associations with neonatal risk

Table 4. Associations between RTFs at 1 and 2 years, and neurodevelopmental outcomes at 2 years.

	1 year					
	RTF Cartoon ($n = 111$)		RTF Motion ($n = 113$)		RTF Form ($n = 102$)	
2 years	B (CI)	R^2	B (CI)	R^2	B (CI)	R^2
Bayley-III cognitive	−4.4 (−7.4;−1.5)	7.2*	−1.0 (−1.8;−0.2)	4.5**	0.2 (−0.2:0.6)	†
Bayley-III total motor	−3.5 (−6.6;−0.5)	4.4**	−0.5 (−1.5;0.5)	†	0.1 (−0.4;0.5)	†
Lexi	0.1 (−4.3;4.4)	†	−0.4 (−1.7;0.8)	†	−0.5 (−1.0;0.1)	†
CBCL total	−0.1 (−2.8;2.6)	†	0.3 (−0.5;1.1)	†	−0.0 (−0.4;0.4)	†
	2 years					
	RTF Cartoon ($n = 141$)		RTF Motion ($n = 151$)		RTF Form ($n = 145$)	
2 years	B (CI)	R^2	B (CI)	R^2	B (CI)	R^2
Bayley-III cognitive	−1.3 (−4.8;2.1)	†	−0.6 (−1.5;0.3)	†	−0.1 (−0.5;0.3)	†
Bayley-III total motor	−0.6 (−5.0;3.7)	†	0.1 (−1.0;1.2)	†	−0.5 (−1.0;0.0)	†
Lexi	2.9 (−1.7;7.4)	†	−0.4 (−1.5;0.7)	†	−0.5 (−1.1;0.1)	†
CBCL total	0.9 (−2.2;4.0)	†	−0.1 (−0.8;0.6)	†	−0.1 (−0.5;0.3)	†

Beta-coefficients (B) are shown per 100 ms, followed by 95% confidence intervals (CI). R^2 is the adjusted proportion of the variance explained, shown as percentage. .
RTF Reaction time to fixation, *Bayley-III* Bayley Scales of Infant and Toddler Development-Third edition, *CBCL* Child Behavior Checklist.
*P value < 0.005.
**P value < 0.05.
†R^2 < 3.0% and P value > 0.05.

Table 5. Added explanatory value of Cartoon and Motion RTFs to a basic neonatal model for prediction of neurodevelopmental outcome at 2 years.

$n = 101$	Basic neonatal model		Neonatal and visuospatial model		Difference	
	R^2	P	R^2	P	ΔR^2	ΔP
Bayley-III cognitive	34.5	**<0.001**	38.4	**<0.001**	3.9	**0.04**
Bayley-III total motor	12.9	**0.02**	12.7	**0.03**	*	0.39
Lexi	14.5	**0.01**	12.8	**0.03**	*	0.75
CBCL total	19.9	**0.001**	18.2	**0.004**	*	0.79

Explanatory value per outcome of the "basic neonatal" model with only neonatal risk factors (sex, GA, combined parental education level, BPD grade, treated PDA, brain injury and total days of hospital admission) and the "neonatal and visuospatial" model (same neonatal risk factors + RTFs for the Cartoon and Motion stimulus at 1 year CA), and the difference (Δ) between the two models. R^2 is the adjusted proportion of the variance explained by each model, shown as percentage. ΔR^2 depicts how much more of outcome variance is explained through adding RTF for both the Cartoon and Motion stimulus at 1 year to the model. Significance levels (P) are given for the proportion of variance explained as well as for the increase in explanatory value (ΔP). Bold numbers indicate $P < 0.05$.
RTF Reaction time to fixation, *Bayley-III* Bayley Scales of Infant and Toddler Development-Third edition, *CBCL* Child Behavior Checklist, *GA* gestational age, *BPD* bronchopulmonary dysplasia, *PDA* persistent ductus arteriosus, *brain injury* intraventricular hemorrhage grade I or II, stroke, cerebral bleeding or periventricular leukomalacia.
*R^2 < 1.0%.

factors. These findings illustrate the complex and multifactorial origin of language and behavior which likely make them more difficult to predict. Very little is known about the relation between language and visuospatial function. Geldof et al. found that visual perceptive dysfunction explained small amounts of variance in verbal IQ (VIQ) when compared to performance IQ (PIQ) at 5 years (13% vs 35%, respectively), and that children with cerebral visual impairment had significantly lower PIQ but not VIQ, as compared to those without cerebral visual impairment.[47,48] This could be explained by the fact that visuospatial function is believed to share neural networks and visual abilities with cognitive performance, but less so with expressive language development.[47] With regard to behavioral outcome, previous eye tracking-based studies in preterm children at an older age showed associations between aberrant gaze patterns[49] or other eye movement errors or delays[50] and psychiatric disorders, diagnosed with the Diagnostic and Statistical Manual of Mental Disorders (DSM). However, the CBCL for 1.5–5 years used in the present study is a screening questionnaire with questionable predictive value for later DSM-related pathology.[51–54] Given these challenges in diagnosing behavioral disorders at the age of 2 years, it would be interesting to follow behavioral performance up to a later age.

No associations between visuospatial attention and processing at 2 years and neurodevelopmental outcome were found. Exploration of the delay patterns suggests that it is mainly the measurement at 1 year that drives the predictive effect. In particular, visuospatial function could be considered an essential factor to normal cognitive development in the following year(s). This implies that visuospatial dysfunction at 2 years may in fact be associated with impaired neurodevelopment later in childhood. Hence, follow-up studies are needed to investigate how the current associations evolve over the course of childhood, especially given the before mentioned limited predictive value of early Bayley-III testing for later IQ performance.[8,9] Another explanation for the absent association at 2 years might be the smaller intra-individual variation in RTFs at 2 years as compared to 1 year. A larger sample size might therefore be needed to reveal subtle associations.

A strength of this study is the large cohort of young preterm children that constitutes a representative sample of the broader preterm population, namely with no, mild or moderate brain

damage, in which neurodevelopment has always been difficult to predict. Another strength of this study is the extensive information on perinatal and neonatal risk factors that allowed for a "basic neonatal" model with high predictive ability. In addition, the reflexive nature of the eye tracking-based paradigm and the fact that results are only obtained when a child actually attends the paradigm means that its parameters (RTFs) are not likely to be influenced by loss of attention, fatigue or lack of motivation. This is an important characteristic because conventional neurodevelopmental test results are generally hampered by such factors.

A limitation of this study is that due to practical reasons, only 85 (41%) of the 209 children underwent visuospatial testing at both 1 and 2 years. This resulted in insufficient statistical power to investigate the visuospatial delay patterns over time in more detail. In addition, translating results into clinical practice requires further research. However, our study may be a stepping stone towards more individualized follow-up programs, needed in times of health-care cuts and development of personalized medicine. The study showed that adding visuospatial attention and processing dysfunction to current criteria for inclusion in neonatal follow-up programs could improve detection of children at risk of adverse neurodevelopment rather than using cut-offs based on neonatal factors alone. In addition to its potential predictive value for general adverse neurodevelopment, adding this quick and easy visuospatial test as a screening tool to neonatal follow-up programs allows for detection of preterm children at risk of (cerebral) visuospatial dysfunction, a neurodevelopmental domain that is currently not incorporated in follow-up programs. Including this domain is of importance, given that the prevalence of children born preterm showing signs of (cerebral) visual (spatial) impairment in the first 5 years of life is high (20–45%).[20,27,48,55]

CONCLUSION

This study showed that visuospatial attention and motion processing function at 1 year is a predictive factor for overall cognitive and motor development 1 year later. This suggests that a quick and easy eye tracking-based assessment can help to identify preterm children at risk of adverse neurodevelopment. Although follow-up studies are needed to investigate how these associations evolve over the course of childhood, this visuospatial method could be a valuable addition to neonatal follow-up programs in the future.

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AUTHOR CONTRIBUTIONS

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ADDITIONAL INFORMATION

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