Pediatric Neurology xxx (xxxx) xxx

Contents lists available at ScienceDirect

Pediatric Neurology

journal homepage: www.elsevier.com/locate/pnu

Research Paper

Brain Damage and Visuospatial Impairments: Exploring Early Structure-Function Associations in Children Born Very Preterm

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ARTICLE INFO

Article history:
Received 30 May 2019
Accepted 21 December 2019
Available online xxx

Keywords:
Structural damage
MRI scoring
Functional assessments
Visuospatial attention
Motion processing
Eye tracking

ABSTRACT

Background: To provide insight into early neurosensory development in children born very preterm, we assessed the association between early structural brain damage and functional visuospatial attention and motion processing from one to two years corrected age.
Methods: In 112 children born at <32 weeks gestational age, we assessed brain damage and growth with a standardized scoring system on magnetic resonance imaging (MRI; 1.5 Tesla) scans performed at 29 to 35 weeks gestational age. Of the children with an MRI scan, 82 participated in an eye tracking-based assessment of visuospatial attention and motion processing (Tobii T60XL) at one year corrected age and 59 at two years corrected age.
Results: MRI scoring showed good intra- and inter-rater reproducibility. At one year, 10% children had delayed attentional reaction times and 23% had delayed motion reaction times. Moderate to severe brain damage significantly correlated with slower visuospatial reaction times. At two years, despite attention and motion reaction times becoming significantly faster, 20% had delayed attentional reaction times and 35% had delayed motion reaction times, but no correlations with MRI scores were found. The presence of structural brain damage was associated with abnormal functional performance over age.
Conclusions: The present study indicates an association between moderate to severe brain damage and visuospatial attention and motion processing dysfunction at one year corrected age. This provides a new perspective on comprehensive MRI scoring and quantitative functional visuospatial assessments and their applicability in children born very preterm in their first years of life.

Introduction

After very preterm birth (i.e., less than 32 weeks gestational age [GA]) there are a large number of complications that lead to (often severe) long-term neurodevelopmental problems in survivors.[1-3] The human brain is especially vulnerable during the third trimester of gestation in which it undergoes some of its biggest growth and development.[4,5] Therefore, children born very preterm are at high risk of disruptions in normal brain development (e.g., abnormal myelination) and brain damage (e.g., intraventricular hemorrhages [IVHs]).[5] Brain damage acquired early in life can lead to neurodevelopmental impairments and can substantially impact further cognitive and academic function.[6] In the past decades several early neuroprotective strategies and (neuro)developmental support programs have been developed.[7-9] Careful selection of children who could benefit from such early interventions may be aided by both structural and functional information on brain development.

To comprehensively assess early macrostructural brain development and overt brain damage, Kidokoro et al.[4] developed a scoring system applicable to a magnetic resonance imaging

Conflicts of interest: None.
Brain damage and visuospatial impairments.
Funding: This work was supported by NOVUM (stichtingnovum.org; grant number OI0342). The study sponsor had no involvement with the study design; data collection, analysis, or interpretation; writing of the report; or the decision to submit the manuscript for publication.
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https://doi.org/10.1016/j.pediatrneurol.2019.12.010

(MRI) scan made at term equivalent age (TEA). The system has been validated for MRI scans made at 29 to 35 weeks GA: the scores of the scans were associated with behavioral and neurodevelopmental outcome at one year corrected age (CA) on the Bayley Scales of Infant and Toddler Development and Neuro-Sensory Motor Developmental Assessment.[10] A disadvantage of these neurodevelopmental tests is that they do not provide information on individual sensory modalities that contribute to a child's development, for example, the somatosensory, auditory, or visuospatial domains.[11] In particular, as visuospatial attention and processing is essential to interact with the environment, impairments in this domain can have substantial negative impact on the development of cognitive, motor, and behavioral skills.[12,13]

A functional test to recognize and acknowledge visuospatial problems early in life has long been missing. To bridge this gap, an eye tracking-based method was developed within our group to quantify visuospatial attention and processing from one year of age. This method employs the measurement of eye movement responses toward specific visual stimuli, which are indicative for visuospatial detection and processing.[14] At one year CA, children born at less than 29 weeks GA without evident brain damage had slower orienting reaction times toward visual stimuli than children born at term.[15] Delayed visuospatial attention and processing was found in 8% to 23% children born between 26 and 32 weeks GA, independent of brain damage.[16] It has not yet been clarified how visuospatial attention and processing relates to the degree and location of brain damage in children born preterm. Another important question is whether early structural MRI scores have predictive value for long-term functional development of individual sensory modalities.[4,10]

The aim of this study was to investigate the association between structural MRI score at 29 to 35 weeks GA and functional visuospatial attention and processing at one and two years CA in children born at less than 32 weeks GA. We hypothesized that there is an association between early structural MRI score and later visuospatial function. We expected our findings to expand the clinical relevance of the early structural MRI assessments and to highlight the importance of early functional visuospatial assessments.

Methods

Participants

The current study is part of a prospective cohort study that was conducted at Erasmus MC-Sophia Children's Hospital, Rotterdam, the Netherlands, from 2011 to 2018. Children born before 32 weeks GA were recruited from the Department of Neonatology after written informed consent of their caregivers. Exclusion criteria were retinopathy of prematurity higher than grade 3 and oculomotor apraxia. From this database with a total of 210 children we retrospectively selected 112 children who had undergone an MRI scan shortly after birth as part of standard clinical procedures. An existing control group of typically developing term-born children without a medical history (e.g., no neurological or visual problems) was used as a reference sample for the visuospatial test (see a previous study for more information[16]). Ethics approval was obtained from the Medical Ethical Research Committee of Erasmus MC, Rotterdam, The Netherlands (MEC-2012-097 and MEC-2016-724). We adhered to the tenets of the Declaration of Helsinki (2013) for research involving human subjects.

Clinical characteristics

Of all included children, information about the following demographic and clinical characteristics were collected from the medical records: gender, multiplets, GA at birth, birth weight (BW), 5-minute Apgar score, postnatal inotropics, patent ductus arteriosus (PDA, if diagnosed and treated), postnatal corticosteroids, postnatal invasive respiratory assistance (based on whether intubation was needed), infant respiratory distress syndrome (IRDS, if treated with surfactant), bronchopulmonary disease (if diagnosed and treated with dexamethasone), necrotizing enterocolitis (if diagnosed and treated), postnatal sepsis (based on clinical signs and treatment), and grade of retinopathy of prematurity.

MRI acquisition

Cerebral MRI was performed without sedation at 30 weeks GA or when the child was medically stable (range 29 to 35 weeks GA) as a part of standard medical care. Children were scanned using a 1.5T MRI scanner, Signa HDxt or SIGNA Explorer (GE Medical Systems, GE Health Care, The Netherlands). Magnetic resonance images were visually checked for quality and were excluded from the analysis if movement impeded reliable analysis. Both T2-weighted sequences (preferably coronal and transversal, single shot/fast recovery fast spin echo) and T1-weighted sequences were used for scoring.

MRI scoring

The MRI scans were scored on brain growth and damage using a modified version of the standardized scoring system of Kidokoro et al.[4] The standardized scoring system was modified on the cerebral white matter (CWM) component because myelination delay and thinning of the corpus callosum were difficult to determine reliably due to the scanning procedure. Scoring was performed after training in neonatal MRI scoring by a researcher specialized in pediatric neuroradiology (J.D.). The raters had no knowledge of the performance of the child on the visuospatial attention test. Appendix Table 1 shows the complete scoring system. MRI scoring was performed using ITK SNAP 2.3.[17]

Appendix Figure 1 shows representative magnetic resonance images from children in the study population with cystic lesions in the CWM, focal signal abnormalities in the CWM, signal abnormalities in the deep gray matter (DGM), and signal abnormalities in the cerebellum. Appendix Figure 2 shows the locations of the five regional brain measurements in the CWM, the cortical gray matter (CGM), the DGM, and the cerebellum: ventricular diameter (right lateral ventricle, left lateral ventricle), biparietal width, interhemispheric distance, DGM area, and transcerebellar diameter.[4] As the size of the structures is partly dependent on GA at scanning due to brain growth, we corrected each scan by using the equations determined by George et al.[10] Appendix Table 2 shows the MRI slices on which the brain regions were measured and the equations that were used to correct for GA at scanning. Based on global MRI score, the children were divided into three different MRI damage classes: normal (global MRI score 0 to 2), mild (global MRI score 3 to 6), or moderate to severe (global MRI score $\geq$ 7).

Variability assessment of MRI scoring

Interrater variability of MRI scoring was tested with 12 MRI scans scored by a second blinded rater. Intrarater variability of MRI scoring was tested with 12 randomly selected MRI scans that were rescored by the first rater (M.M.v.G.) two weeks after initial scoring.

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Scoring of intraventricular hemorrhage and periventricular leukomalacia

In addition to MRI scoring, the grade of IVH right and left (according to Papile classification[18]) and the grade of periventricular leukomalacia (PVL) right and left (based on Chao et al.[19]) were scored separately for each child. The maximum score of IVH right/left was 4 and for PVL right/left was 3.

Visuospatial attention and processing assessment

All children participated in a visuospatial attention and processing assessment that was performed by researchers who were unaware of the MRI findings. During this assessment, several visual stimuli were presented on a 24-inch monitor, while eye movements were simultaneously recorded with an integrated eye tracking system sampling at 60 Hz (Tobii T60XL; Tobii Corporation, Danderyd, Sweden). The assessment took place in a quiet room in Sophia Children's Hospital during a regular follow-up appointment of the child at the outpatient clinic of neonatology. For a detailed description of the assessment we refer to previous work in children born preterm.[15] For the present study, we selected two visual stimuli that previously showed abnormal results in children born preterm at one year CA and were therefore most clinically relevant[15,16]:

1. Cartoon: a movie of a colorful, high-contrast, slowly oscillating cartoon picture (reproduced with permission from Dick Bruna, Mercis BV, Amsterdam, The Netherlands) with a visual angle of 4.5° × 9.0° (width × height) moving 1.5° up and down at 3°/s, against a black background.[20] Cartoons were shown 16 times per test sequence.
2. Local Motion: a movie containing a black-and-white patterned square target, with a visual angle of 2.3°, against an equally patterned background, moving 2.5° to the left and to the right at 2.5°/s.[20] Motion stimuli were shown four times per test sequence.

Eye tracking data processing and analysis

The eye tracking data were analyzed using a custom MATLAB script (Mathworks Inc, Natick, MA, USA). Per stimulus presentation it was determined whether the child had seen it (i.e., whether gaze was in the stimulus' target area for at least 200 ms). If seen, the reaction time to fixation (RT) was calculated: the time from stimulus presentation until gaze entered the target area.[14] From all separate RTs of a single child toward one stimulus type, three different RT components were calculated: the RT_{min}, RT_{var}, and reaction time to fixation (RTF). First, of all the reliable RTs (at least four for cartoon, at least one for motion[21]), a cumulative plot was made. To this cumulative plot, an exponential curve was fitted to quantify the RTF as the minimum RT (RT_{min}) together with one-third of the time constant of the exponential curve (RT_{var}). RT_{min} represents the fastest RTF of a child toward that particular stimulus type. RT_{var} represents the variability in RTs toward that particular stimulus type. The sum of RT_{min} and RT_{var}, that is, RTF, reflects the average processing speed plus eye movement execution time of that particular stimulus type.[20]

The RTF values of the children born very preterm were compared with the RTF values of age-matched typically developing term-born children, adopted from an existing normative database.[20] Cutoff points were set at the mean + 2 S.D. (i.e., 95% confidence interval) of the normative RTF values: for cartoon these values were 353ms at one year CA (n = 39) and 290ms at two years CA (n = 61); for motion these values were 1022ms at one year CA (n = 21) and 615ms at two years CA (n = 35). RTF values above these cutoff points were denoted as abnormal/delayed. Changes in RTF values compared with the normative references from one to two years CA were analyzed. This analysis resulted in four groups: children with normal RTF compared with the norms at one and two years CA (normal-stable), children with abnormal RTF at both ages (abnormal stable), children who changed from normal RTF at one year to abnormal at two years CA (deteriorated), and vice versa (normalized). Clinical characteristics and structural MRI scores were compared between these four groups.

Statistical analysis

Intra- and inter-rater variabilities of MRI scoring were evaluated with two-way mixed intraclass correlation coefficients. Agreement was evaluated by the percentage level of accuracy: the exact score ±1 for subscores and the exact score ± 2 for global scores. The MRI scores and RT components were not normally distributed (Kolmogorov-Smirnov tests P value < 0.05). Consequently, nonparametric statistical tests were performed. Differences in MRI global scores, subscores, and IVH and PVL grades between the groups with an eye tracking measurement at one and two years CA were evaluated with the Kruskal-Wallis test. We used Spearman's correlation coefficients to evaluate the association between IVH and PVL grade and MRI global scores and subscores. We calculated partial correlation coefficients between MRI scores and RT components at one and two years CA, to control for the effect of GA and BW on these correlations. We applied a Bonferroni correction for multiple comparisons (P value of $0.05/5 = 0.01$). Differences in RT components and changes between MRI damage classes for both stimuli were evaluated with Kruskal-Wallis tests with posthoc two-sided Mann-Whitney U tests. We performed Wilcoxon signed-rank tests to analyze changes in RTF component values for cartoon and motion from one to two years CA. Between the groups with various types of changes in functional visuospatial performance, chi-square tests were used to compare the prevalence of clinical characteristics, and Kruskal-Wallis tests with posthoc Mann-Whitney U tests were used to analyze differences in GA, BW, and structural MRI scores. All analyses were performed using IBM SPSS Statistics 24 (IBM Corporation, Armonk, NY).

Results

Participants

Baseline clinical characteristics of the total group of included children are summarized in Table 1. MRI scans were obtained from 112 children (52% male, mean [S.D.] GA at birth = 27.2 [1.7] weeks, mean [S.D.] BW = 996 [280] g). Of the children with an MRI scan, 82 children (73%) participated in the eye tracking assessment at one year CA, and 59 children (53%) at two years CA. Prevalent clinical factors in the overall group were intubation (73%), IRDS (64%), and PDA (48%).

MRI scores

The median [interquartile range] global MRI score = 4 [2 to 6], CWM score = 2 [1 to 3], CGM score = 0 [0 to 0], DGM score = 2 [0 to 2], and Cerebellum score = 0 [0 to 1], for children at one year CA. Median MRI scores did not significantly differ between the children with a visuospatial assessment at one year and at two years CA.

MRI scoring reliability

The MRI score showed good reproducibility between and within raters, as shown in Appendix Table 3.

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TABLE 1
Clinical Characteristics of the Children Born Preterm

Clinical Characteristics	All Children (n = 112)	MRI and Eye Tracking at 1 Year CA (n = 82)	MRI and Eye Tracking at 2 Years CA (n = 59)
GA at birth (weeks)	27.2 (1.7)	26.9 (1.4)	27.4 (1.7)
Birth weight (g)	996 (280)	964 (242)	1022 (303)
Male sex	58 (52%)	44 (54%)	32 (54%)
Multiplets	36 (32%)	30 (37%)	19 (32%)
5-min Apgar score	7 [6-9]	8 [6-9]	7 [6-8]
Inotropics	20 (18%)	16 (20%)	10 (17%)
PDA	54 (48%)	43 (52%)	28 (48%)
Corticosteroids	19 (17%)	15 (18%)	9 (15%)
Intubation	82 (73%)	65 (79%)	40 (68%)
IRDS	72 (64%)	56 (68%)	35 (59%)
BPD	48 (23%)	18 (22%)	15 (25%)
NEC	7 (6%)	6 (7%)	3 (5%)
Sepsis	44 (39%)	37 (45%)	20 (34%)
ROP (grade, ≤3)	0 [0-0]	0 [0-0]	0 [0-0]

Abbreviations:
BPD = Bronchopulmonary dysplasia
CA = Corrected age
GA = Gestational age
IRDS = Infant respiratory distress syndrome
MRI = Magnetic resonance imaging
NEC = Necrotizing enterocolitis
PDA = Patent ductus arteriosus
ROP = Retinopathy of prematurity
Values represent average (S.D.), median [interquartile range], or frequency (%).

Appendix Table 4 summarizes correlations between MRI scores and IVH and PVL grade. The results show that IVH is mainly represented in the CWM and DGM scores, and that PVL is mainly represented in the CWM score.

RT components at one year and two years CA

Reliable visuospatial results (i.e., at least four cartoons detected[21]) were obtained for 70 of the 82 children at one year CA (85%) and for 47 of the 59 children at two years CA (80%). Overall, RTF values significantly decreased from one to two years CA: on average −44 (95) ms for cartoon ($Z = -2.43$, $P = 0.015$) and −130 (424) ms for motion ($Z = -2.30$, $P = 0.021$). Figure shows the individual RTF values of children born preterm for cartoon and motion, against their age and per MRI damage class. Compared with the term-born control group (represented by dashed lines), 14 (23%, n = 62) children at one year CA and nine (20%, n = 45) at two years CA showed delayed RTF for cartoon; six (10%, n = 60) children at one year CA and 18 (35%, n = 51) at two years CA showed delayed RTF for motion.

Correlation of RT components and RT changes with MRI score

Table 2 summarizes the partial correlations between RT components and MRI score at one year and two years CA, controlled for BW and GA (BW significantly correlated with Global score [$r_s = -0.25$, $P = 0.01$] and both GA and BW significantly correlated with Cerebellum score [$r_s = -0.29$, $P = 0.002$ and $r_s = -0.35$, $P = 0.000$]). At one year CA, RTF and RT_{min} for cartoon positively correlated with CGM score ($r = 0.37$; $P = 0.004$ and $r = 0.40$; $P = 0.003$) and RTF positively correlated with CWM ($r = 0.32$; $P = 0.009$). RT_{min} and RTF for motion positively correlated with CWM, DGM, and Cerebellum scores (r ranging from 0.29 to 0.35, all $P < 0.01$). RT components for cartoon and motion at two years CA and the absolute changes in RTF values from one to two years CA (not shown in Table 2) did not significantly correlate with MRI scores.

Differences in RTF components and changes between MRI damage classes

A significant difference between MRI damage classes was found for RT_{min} and RTF motion at one year CA ($H(2) = 11.95$, $P = 0.003$ and $H(2) = 9.29$, $P = 0.01$), and a trend was found for RTF cartoon at one year CA ($H(2) = 4.77$, $P = 0.092$). RT_{min} and RTF motion and RTF cartoon were significantly slower in the moderate to severe MRI damage class than in the normal ($U = 81$, $r = -0.44$, $P = 0.006$, $U = 102$, $r = -0.34$, $P = 0.03$, and $U = 107$, $r = -0.32$, $P = 0.046$) and mild MRI damage class ($U = 56$, $r = -0.52$, $P = 0.002$, $U = 64$, $r = -0.47$, $P = 0.005$, and $U = 100$, $r = -0.31$, $P = 0.056$). One year changes in RTF cartoon and motion did not significantly differ between MRI damage classes. Table 3 summarizes RTF cartoon and RTF motion scores between the MRI damage classes normal, mild, and moderate to severe.

Differences in clinical and structural scores between groups with functional one-year changes

Table 4 shows for the four change groups (normal-stable, abnormal-stable, normalized, and deteriorated) the prevalence of clinical characteristics and the structural MRI scores. The presence of inotropics was higher in the groups with abnormal-stable and normalized performance for cartoon (marginally significant; cartoon $\chi^2 = 7.79$, $P = 0.05$). In addition, a relatively large number of children in these groups (50% to 100%) had the clinical factors PDA, intubation, IRDS and bronchopulmonary disease. These groups also had relatively high MRI global, CWM, DGM, Cerebellum, and IVH scores compared with the children in the normal-stable and deteriorated groups, but these differences were not statistically significant.

Discussion

The results of the present study suggest that early structural brain assessments are associated with cerebral visuospatial function in the first year of life. This translates into a related association with functional visuospatial changes compared to normative references from one to two years CA. Especially children with moderate to severe brain damage seem to be at risk of visuospatial attention and motion processing dysfunction at one year CA. After that age, their functional performance predominantly remained abnormal or normalized. Both patterns also seemed related to perinatal clinical risk factors for cardiovascular and/or respiratory failure. The fact that we did not find any correlations at two years CA implies that the association between early brain macrostructure and brain function in the visuospatial domain may not be clinically relevant after the first year of life in very preterm-born children. However, it is well known that children born preterm are at high risk of growing into deficit in multiple neurodevelopmental domains at later developmental stages, for example, at preschool[22] and school age.[23,24] Moreover, our results showed that the rate of abnormalities compared with normative age-related visuospatial development increased, despite the finding that overall attentional and motion RTs from one to two years CA became faster; this warrants a longer and more elaborate follow-up than the one presented here. Taken together, our findings provide a new perspective on comprehensive MRI scoring and quantitative functional visuospatial assessments and their applicability in the very preterm population in the first years of life.

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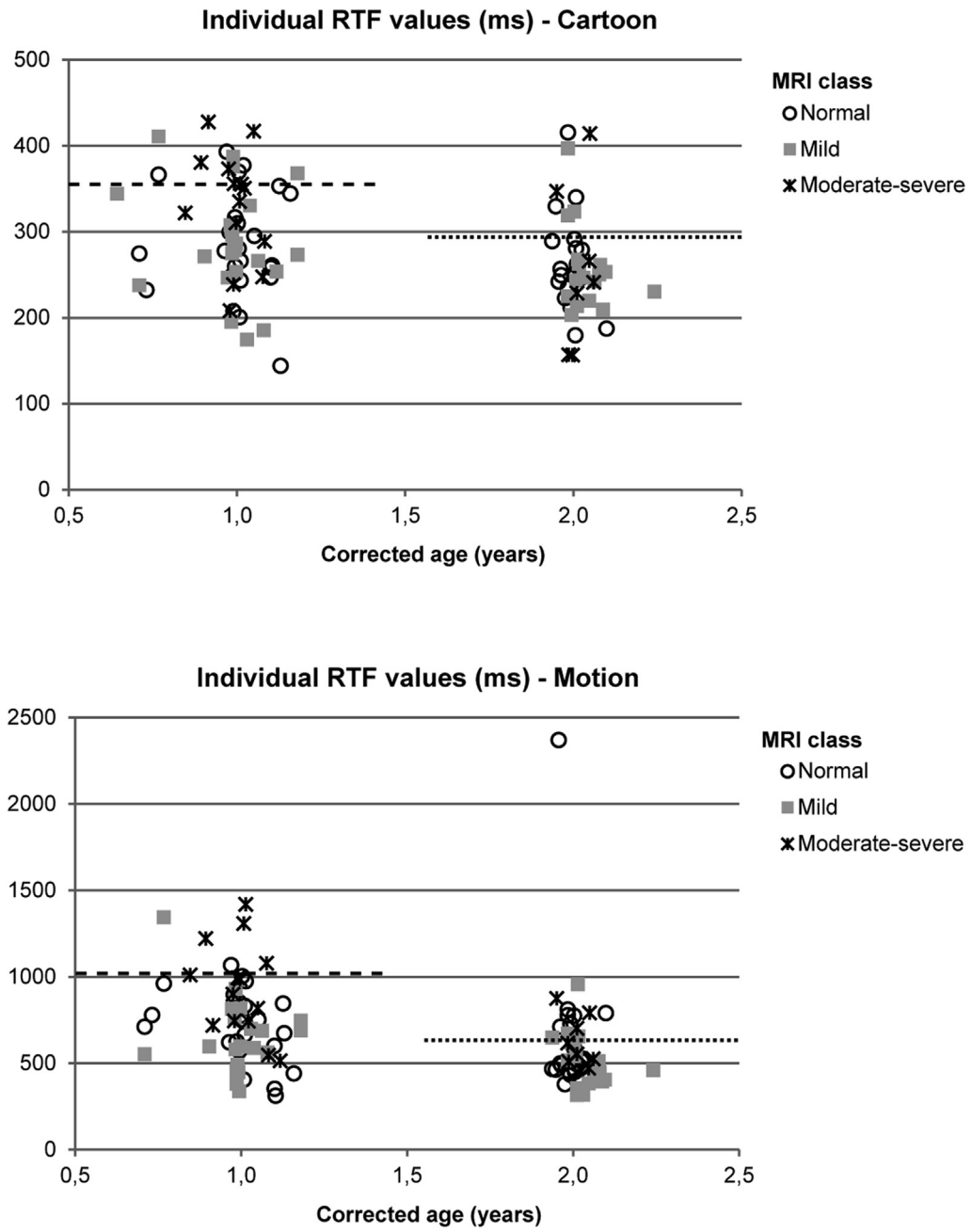

FIGURE. Scatter plot of RTF values for cartoon (upper panel) and motion (lower panel) of individual preterm children. The x-axis represents age in years CA, and the y-axis represents the RTF value in ms. The symbols represent the MRI damage classes normal (circle), mild (square), or moderate-severe (star). The coarsely dashed line represents mean + 2 S.D. of the term-born control group at one year CA, the finely dashed line represents mean + 2 S.D. of the term-born control group at 2 years CA. Note the difference in y-axis values between panels. CA, corrected age; MRI, magnetic resonance imaging; RTF, reaction time to fixation.

Clinical advantages of early MRI scoring

The prevalence of preterm birth is increasing globally, and it is a leading cause of neurodevelopmental impairment in childhood. Because of ongoing improvements in both fetal and neonatal care, the survival rates of infants born very preterm are gradually improving. Following preterm birth, the major goal of clinical care is to support the child in his or her development that normally would have taken place in the uterus.[6] Owing to immaturity, preterm-born children are at high risk of damage to and developmental problems of the brain.[5,6,25] Structural MRI scoring to quantify brain damage and growth has found its way to clinical practice.[4,10,26-28] Our study used the structural MRI scoring method for MRI scans made at 29 to 35 weeks GA.[10] Due to the limited quality of our scans, it was not possible to reliably measure the corpus callosum or to assess myelination correctly.[4,10]However, their exclusion did not lead to a low inter- and intrarater variability or agreement, suggesting that the structural MRI scoring system is also applicable to scans of lower quality. Moreover, we showed that the structural MRI scoring system positively correlated with the conventional grading of IVH and PVL in our preterm population; this indicates that a scoring method that evaluates more brain regions still takes into account the impact of IVH and PVL. The possibility to score lower-quality scans, the high inter- and intrarater

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TABLE 2
Partial Correlation Coefficients Between MRI Scores and the Three RTF Components for Cartoon and Motion at One Year and Two Years CA, Controlled for BW and GA at Birth

MRI Score	r_s RTF Cartoon	r_s RT_{min} Cartoon	r_s RT_{var} Cartoon	r_s RTF Motion	r_s RT_{min} Motion	r_s RT_{var} Motion
n = 82						
1 year CA						
Global	0.30	0.21	0.14	0.29	0.32	−0.12
CWM	0.32*	0.25	0.10	0.31*	0.31	0.01
CGM	0.37*	0.40*	−0.09	0.10	0.12	−0.09
DGM	0.30	0.22	0.13	0.35*	0.35*	−0.00
Cerebellum	0.11	0.12	−0.02	0.34*	0.30	0.12
n = 59						
2 years CA						
Global	−0.04	−0.09	0.13	−0.03	−0.04	0.09
CWM	−0.10	−0.12	0.02	0.02	−0.01	0.14
CGM	−0.31	−0.28	−0.12	−0.17	−0.17	0.18
DGM	0.08	0.07	0.05	−0.02	−0.04	0.10
Cerebellum	0.12	0.03	0.25	−0.02	−0.02	−0.03

Abbreviations:
BW = Birth weight
CA = Corrected age
CGM = Cerebral gray matter
CWM = Cerebral white matter
DGM = Deep gray matter
GA = Gestational age
MRI = Magnetic resonance imaging
RTF = Reaction time to fixation
* Statistically significant correlations (partial correlation coefficient $P < 0.01$).

variability in newly trained raters, and the strong positive correlation with IVH and PVL grade increases the clinical value of structural MRI scoring and facilitates its usage in clinical practice.

According to de Vries and Cowan, scoring systems as the one used in the current study should be used with care. The authors proposed that some typical findings in the preterm brain, such as connatal cysts and germinal matrix hemorrhages, can easily be mistaken for severe brain injury, leading to a disproportionately high MRI score.[29] These pitfalls should be taken into account when assessing brain scans at such an early age. Reviewing routine ultrasound scans of the study population and consulting medical specialists with extensive experience in neonatal neuroimaging can reduce these misclassifications.

Visuospatial consequences of very preterm birth

The cerebral visual system is susceptible to the typical brain injuries related to preterm birth, such as PVL and IVH. The locations of these injuries overlap with, for example, the optic radiations. The white matter connections of the ventral stream run along the inferior horns of the lateral ventricles, which can be affected in case of IVH and posthemorrhagic hydrocephalus.[30-33] Early damage to the developing brain may cause injury to the preoligodendrocytes, which can lead to impaired thalamocortical myelination. All these injuries may impact the connections between primary and secondary visual cortices and between sensory and motor visual function, eventually leading to cerebral visual impairments (CVIs) and delayed visuospatial reaction times.[34-36]

A previous study showed a correlation between severity of brain damage on MRI and performance of children on a functional vision test at age one to six years.[37] Enlarged lateral ventricles with an irregular border are found in children with CVI and a history of PVL.[34,38-40] However, this finding is not pathognomonic for CVI.[41] There are indications that children with normal MRI findings have a different CVI profile than children with MRI abnormalities, suggesting different etiologies of CVI.[41]

After very preterm birth, not all children suffer from brain damage or growth impairments.[42,43] However, this does not guarantee that visuospatial attention and processing development will be comparable to typically developing children.[15] In our cohort at two years CA, a substantial number (20% to 35%) of children born very preterm had orienting reaction times of more than 2 S.D. above the normative mean value, irrespective of their brain damage (Figure). This finding suggests that very preterm born children remain at risk of visuospatial problems at two years CA and gives a longer-term perspective on the visuospatial dysfunctions that were previously found at one year CA.[15]

TABLE 3
Average RTF for Cartoon and Motion per MRI Damage Class at One Year and Two Years CA

MRI Damage Class	1 Year CA		2 Years CA	
	RTF Cartoon	RTF Motion	RTF Cartoon	RTF Motion
Normal	283 (61) (n = 25)	721 (200) (n = 25)	262 (53) (n = 21)	637 (393) (n = 24)
Mild	287 (62) (n = 23)	661 (220) (n = 21)	257 (49) (n = 17)	523 (160) (n = 19)
Moderate-severe	328 (65) (n = 14)	927 (271) (n = 14)	258 (95) (n = 7)	629 (145) (n = 8)
P value	0.092	0.01	0.834	0.143

Abbreviations:
CA = Corrected age
MRI = Magnetic resonance imaging
RTF = Reaction time to fixation
Values represent average (S.D.) in ms. *P* values < 0.05 indicate statistically significant differences in scores between MRI damage classes.

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TABLE 4
Clinical Characteristics and Structural MRI Scores Shown for the Groups of Children With Various Changes in Visuospatial Results From One to Two Years CA, Compared With Normative References

Cartoon Changes (N = 26)	Normal-Stable (N = 15)	Abnormal-Stable (N = 1)	Normalized (N = 6)	Deteriorated (N = 4)
Clinical characteristics (mean, S.D., or prevalence %)				
GA	27.1 (1.4)	28.4 (-)	26.2 (1.1)	27 (1.6)
BW	904 (255)	840 (-)	890 (221)	1064 (210)
Gender (% male)	60%	100%	83%	25%
Inotropics	13%	100%*	50%*	0%
PDA	47%	100%	83%	75%
Intubation	67%	100%	100%	50%
IRDS	47%	100%	83%	50%
BPD	20%	0%	50%	25%
Structural MRI scores [median, IQR]				
Global score	2 [0.75-4]	7 [7-7]	5 [1-9]	2.5 [0.5-6.75]
CWM (range 0-11)	2 [0-2]	3 [3-3]	2 [1-5.25]	2 [0.5-2.75]
CGM (range 0-8)	0 [0-0]	0 [0-0]	0.5 [0-2]	0 [0-0]
DGM (range 0-6)	0 [0-1]	2 [2-2]	1 [0-3]	0.5 [0-2.5]
Cerebellum (range 0-6)	0 [0-1]	2 [2-2]	1 [0-1]	0 [0-1.5]
IVH	0 [0-1]	2 [2-2]	0.5 [0-1.75]	1 [0.25-1.75]
PVL	0 [0-0]	0 [0-0]	0 [0-0.75]	0 [0-0]
Motion Changes (N = 29)	**Normal-Stable (N = 17)**	**Abnormal-Stable (N = 3)**	**Normalized (N = 1)**	**Deteriorated (N = 8)**
Clinical characteristics (mean, S.D., or prevalence %)				
GA	26.9 (1.6)	27 (2)	26.4 (-)	27.4 (0.7)
BW	926 (269)	943 (242)	950 (-)	1098 (216)
Gender (% male)	65%	67%	100%	50%
Inotropics	24%	33%	100%	0%
PDA	59%	100%	100%	50%
Intubation	77%	100%	100%	63%
IRDS	59%	100%	100%	38%
BPD	24%	33%	0%	13%
Structural MRI scores [median, IQR]				
Global score	2 [1-4.75]	7 [6 -]	-	2 [1.25-3.75]
CWM (range 0-11)	2 [0.5-2]	3 [3 -]	5 [5-5]	1.5 [1-2]
CGM (range 0-8)	0 [0-0]	0 [0-0]	2 [2-2]	0 [0-0]
DGM (range 0-6)	0 [0-1.5]	2 [1 -]	-	0 [0-1.75]
Cerebellum (range 0-6)	0 [0-1]	2 [1 -]	1 [1-1]	0 [0-0.75]
IVH	0 [0-1]	2 [1 -]	1 [1-1]	0 [0-1]
PVL	0 [0-0]	0 [0-0]	3 [3-3]	0 [0-0]

Abbreviations:
BPD = Bronchopulmonary dysplasia
BW = Birth weight
CA = Corrected age
CGM = Cerebral gray matter
CWM = Cerebral white matter
DGM = Deep gray matter
GA = Gestational age
IQR = Interquartile range
IRDS = Infant respiratory distress syndrome
IVH = Intraventricular hemorrhage
MRI = Magnetic resonance imaging
PDA = Patent ductus arteriosus
PVL = Periventricular leukomalacia
RTF = Reaction time to fixation
Stable = no changes in RTF relative to normative age-related changes.
* Difference in prevalence of this factor between groups (chi-square test, $P = 0.05$).

We investigated three different parameters to operationalize visuospatial function, but mainly RTF and RT_{min} were responsible for the differences between children with different degrees of brain damage. This finding indicates that the timing of visual-attentional processing is the defining dysfunctional factor, and that reaction time variability plays a smaller role. Because visuospatial functions are essential for optimal learning, having visuospatial attention and processing problems early in life can substantially impact a child's future development.[12,13] Preterm birth has been found to negatively affect sensory processing and quality of life at age 10 years.[44,45] The current results indicate that the negative effects of preterm birth on sensory processing in the visuospatial domain can already be seen at an early developmental stage; this may facilitate the selection of children for rehabilitation interventions early in life, enhancing opportunities for children's further development.[46,47]

Clinical implications of early recognition of children at risk

The finding that more severe brain damage was associated with slower orienting reaction times at one year CA, but not at two years CA and not with deterioration of visuospatial function over the course of one year, may indicate that the clinical value of brain macrostructure of very preterm-born children is limited in the context of visuospatial function development. The explorative results in the small groups of children with both abnormal structural and functional findings show a tendency for these children to either remain at risk (i.e., show consistent delays in these functions over the course of one year early in life) or to normalize functional performance. Previous studies in this field compared a similar MRI scoring system at TEA with neurodevelopmental outcome at 1.5 to 2.5 years CA.[4,10,48-51] Some found that brain growth and injury at

Please cite this article as: van Gils MM et al., Brain Damage and Visuospatial Impairments: Exploring Early Structure-Function Associations in Children Born Very Preterm, Pediatric Neurology, https://doi.org/10.1016/j.pediatrneurol.2019.12.010

30 weeks GA and at TEA was (independently) associated with cognitive and motor performance later in life, whereas others found that the prognostic value of neonatal brain imaging was limited.[48-52] The conflicting results of these studies suggest that brain macrostructure does not fully predict the functional outcome of the child, a fact that impedes the early recognition of children at risk of developmental problems. Combining functional MRI with diffusion tensor imaging (DTI) would provide more information about the relation between brain microstructure and functional brain connections. For example, in-depth analysis of white matter connections in two patients with CVI showed a reduction of white matter fibers in the posterior occipital cortex and of three important visual fasciculi.[38] This observation is in line with the findings of Bassi et al.[53] that visual function in young children is related to white matter development of the optic radiations. Hence, whereas collection of MRI scans and the concurrent scoring method is highly feasible in clinical practice, microstructural connectivity measurements may add more information on a developmental neuroscientific level.

An alternative explanation for the lack of an association between brain structure and function at two years CA and with one-year changes in our study population is brain plasticity. Brain plasticity could, in theory, be supported by specific rehabilitation programs that focus on the visuospatial problems that a particular child experiences. At present, direct evidence for the effectiveness of rehabilitation to support visual and cognitive development is lacking. Review studies failed to draw clear conclusions because articles discussing such programs mostly consisted of case reports.[54,55] Research into neuroprotective interventions early in life leads to more clear conclusions: antenatal corticosteroids to prevent developmental delays and antenatal magnesium sulfate to prevent gross motor dysfunction showed significant effect sizes of 0.49 (95% confidence interval 0.24 to 1.00) and 0.61, respectively (95% confidence interval 0.44 to 0.85).[56] In addition, the generally improved neonatal intensive care has resulted in a decrease in the prevalence of cerebral palsy,[57] which is strongly related to CVI.[39,40]

Study limitations

First, MRI scoring was done retrospectively and depended on the performed MRI sequences as part of clinical neonatal care. Practically, this meant that MRI was only routinely performed around 29 to 35 weeks GA (not at TEA) and that only medically stable children were scanned. In addition, from some children no T2 sequence was available, which made it more difficult to measure brain structures. To minimize the influence of this disadvantage, brain regions that were too difficult to measure were excluded from analysis. In addition, our scans were of limited quality due to reduced magnetic field strength (1.5T), motion artifacts (because of sedation-free scanning), and the limited amount of MRI sequences. Nevertheless, performing MRI scoring on scans that are made during standard clinical care emphasizes and increases the clinical relevance of the findings. Second, in our study population and with the available scans, only one child showed severe brain damage. Therefore, the relevance of our results applies to the large group of children born less than 32 weeks with no, mild, or moderate brain damage. Although our results showed various correlations between brain damage on MRI and visuospatial function at one year CA, it would be worth exploring if these correlations were stronger if there were more children with severe brain damage in the study population; this would tell us whether there is a certain threshold of brain damage before visuospatial delays occur. A major limitation of our longitudinal results is that they were based on a small sample size. As a data integrity check we performed the same analyses as we did for the total study population also in the small longitudinal group and found that the clinical characteristics and structural and functional outcomes were similar. Therefore, even though these exploratory longitudinal results warrant a follow-up, we assume they can be representative of the very preterm population. Last, we assessed functional visuospatial performance only in the domains of general visuospatial attention and motion processing, because these dysfunctions were previously found in children born very preterm. To investigate the full spectrum of neurodevelopment in specific sensory domains, a broader range of visual, spatial, and other sensory functions should be taken into account during quantitative functional assessments.

Conclusion

The current study showed that the structural MRI scoring system first described by Kidokoro et al.[4] can be reliably performed by newly trained users. MRI scores positively correlated with quantitative and functional parameters of visuospatial attention and motion processing at one year CA and with concurrent one-year changes, but not at two years CA. Despite improved functional visuospatial performance from one to two years CA, the amount of children showing reaction time delays compared with normative age-related development increased. Taken together, these results suggest an association between brain structure and function at one year CA in the visuospatial attention and motion processing domain. The risk of visuospatial dysfunctions was highest for preterm children with moderate to severe structural brain damage. Our findings highlight the clinical relevance of comprehensive MRI scoring and of quantitative visuospatial assessments in children born very preterm in their first years of life.

Acknowledgments

The authors are grateful to all children and their parents for their participation. The authors thank Merel Roelen for her support in scoring and analyzing MRI scans; Mark Vonk, Anne van der Linden, Amra Zeric, and Annika Post for their help in data collection and analysis; and the Neonatology department of Sophia Children's Hospital for clinical and logistic support.

Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.pediatrneurol.2019.12.010.

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Please cite this article as: van Gils MM et al., Brain Damage and Visuospatial Impairments: Exploring Early Structure-Function Associations in Children Born Very Preterm, Pediatric Neurology, https://doi.org/10.1016/j.pediatrneurol.2019.12.010