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Linking integrity of visual pathways trajectories to visual behavior deficit in very preterm infants

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ABSTRACT

Low-risk premature infants often develop visual deficits, even in the absence of ophthalmological complications and high-graded brain injury. These complications can be explained by the nature of subtle perinatal lesions and alterations of brain growth due to the prematurity. Subtle brain injuries and vulnerability of axonal pathways can be observed in spatiotemporal context of the white matter segments. The aim of this study was to examine the link between MRI quantitative (*brain metrics* data) and qualitative features (visibility of 2nd white matter segment - sagittal strata and periventricular crossroads C1-C6) and visual behavior in preterm neonates at term-equivalent age. Seventy-one very preterm infants without high-graded brain injury on MRI and no ocular pathologies were studies. The infants received MRI scans at term-equivalent age. MRI scans were analyzed using (a) simple brain metrics and (b) scoring the visibility of transient structural patterns (sagittal strata and periventricular crossroads). At the median age of 41^{+5} PMA weeks infants completed the Neonatal Visual Assessment. Results indicated that visibility of temporal crossroad area C6 and frontal and occipital sagittal strata was positively correlated with visual tracking skills in neonatal period. Furthermore, the visibility of frontal and occipital sagittal strata were strong predictors of total Neonatal Visual Assessment score. The findings confirmed that sagittal strata and periventricular crossroads prominence is a valuable additional marker in perinatal neuroimaging at term-equivalent age. Thus, alteration in MRI appearance of temporal crossroad and sagittal strata may be useful in predicting of visual behavior for very premature born infants.

1. Introduction

Very preterm infants born at very low gestational age (≤ 32wks) and very low birth weight (VLBW; ≤ 1500 g) are at risk of

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developing visual impairments, including deficits in acuity, contrast sensitivity, stereopsis, motion perception, and tracking behavior (MacKay et al., 2005; O'Connor et al., 2004). Although cerebral white matter injury in very preterm infants often affects visual functions (Guzzetta, Cioni, Cowan, & Mercuri, 2001), some very preterm infants without evident or high-grade brain injury on conventional magnetic resonance imaging (MRI) at term-equivalent age also have adverse outcomes in visual perception (Bassi et al., 2008; Berman et al., 2009).

The neurobiological basis of these issues remains poorly understood. A proposed explanation for the visuoperceptual impairments found in very preterm infants is that preterm birth, even in the absence of high-grade brain injury, alters the typical maturational trajectories of visual processing pathways (Leung, Thompson, Black, Dai, & Alsweiler, 2018), and group level studies using MRI have revealed alterations to white matter associated with problems in perceptual function (Ment, Hirtz, & Hüppi, 2009; Miller & Ferriero, 2009). Another reason behind poor visual functioning in low-risk premature infants may be within the severity spectrum of white matter injury, precisely mild/indeterminate category that consists of focal microscopic necrosis (Pierson et al., 2007; Volpe, 2017). These focal lesions are too small to be visualized by conventional MRI, and they may be principally undetected.

Despite using sophisticated MRI methods combined with volumetric measurements, predicting visual functioning in premature infants with no ophthalmologic complications and apparent brain injury is still puzzling. This poses the challenge of finding other imaging markers for adverse outcomes in visual functions, detecting those low-risk very preterm infants early, and offering them timely and domain-specific support for optimal visual outcomes.

In an endeavor to answer this relevant question in clinical neuroscience, we started a long-term project for a cohort of preterm-born infants. Next to the conventional method of assessing brain injury (Kidokoro, Neil, & Inder, 2013), we have applied extended scoring of transient fetal brain patterns, namely periventricular crossroads of pathways, and sagittal strata.

Periventricular axonal crossroads and sagittal strata (Sachs, 1892; Von Monakow, 1905), or constituents of white matter segment II, are becoming recognized as potential predilection sites for hypoxic-ischemic damage in the fetal and neonatal period (Kostović, & Jovanov-Milošević et al., 2014; Kostović, & Kostović-Srzentić et al., 2014). Namely, periventricular crossroads (C1-C6) represent complex crossroads of growing commissural, projection, and associative axonal pathways embedded into an abundance of extracellular matrix and axonal guidance molecules (Judaš et al., 2005). It is also important to notice that the two most frequent pathologies occur at the crossroads site; one is periventricular hemorrhage and the other is periventricular leukomalacia.

Sagittal strata are bilateral parasagittally oriented white matter fiber system consisting of commissural, projection, and associative pathways, and with periventricular crossroads constitute an important maturational stage in transforming transient fetal zones/ white matter segments into the adult form of white matter. Thus, considering their content and spatio-temporal developmental dynamics, their importance in evaluating subtle white matter injuries does not surprise (Judaš et al., 2005; Kostović, & Jovanov-Milošević et al., 2014; Kostović, Kostović-Srzentić, Benjak, Jovanov-Milošević, & Radoš, 2014; Žunić Išasegi et al., 2018; Katušić, Raguž, & Žunić Išasegi, 2020; Katušić & Žunić Išasegi et al., 2020; Kostović Srzentić, Raguž, & Ozretić, 2020; Milos et al., 2020). These transient fetal brain structures have been elaborated within MRI brain exams to score cerebral maturation in preterm infants at term-equivalent age (Pittet, Vasung, Huppi, & Merlini, 2019), but only recently as an comprehensive scoring system concerning the clinical outcome (Katušić & Raguž et al., 2020; Katušić & Žunić Išasegi et al., 2020; Kostović Srzentić et al., 2020; Goeral et al., 2021). Despite that, the existence and visibility of transient fetal brain patterns are still not considered in standard clinical practice in pediatric neuroradiology as a diagnostic tool.

Also, various disturbances during brain development can lead to reduced volumes of cerebral and cerebellar structures and consequently affect neurological and cognitive performance in infancy, childhood, or even early adulthood (Keunen et al., 2012). Unfortunately, precise observer-independent automatic software for MRI-volumetric analysis of neonatal brain is still not available due to the challenges of developing brain imaging (Dubois, Adibpour, Poupon, Hertz-Pannier, & Dehaene-Lambertz, 2016; Katušić & Raguž et al., 2020; Katušić & Žunić Išasegi et al., 2020). Nevertheless, brain metrics, provides us valuable data about the developmental dynamics of brain structure volumes (Tich et al., 2009). Brain metrics is a simple quantitative MRI technique that measures brain structure volumes, and it differs from fetal biometrics which are antenatal ultrasound measurements that are used to indirectly assess the growth and wellbeing of the fetus (Hatab, Zaretsky, Alexander, & Twickler, 2008). Thereby, brain metrics give us information about brain growth disturbances and deviations, which can be related to further neurological and cognitive outcomes, especially valuable in cohorts of prematurely born infants (Eeles et al., 2017; Garel, Chantrel, Elmaleh, Brisse, & Sebag, 2003; Hammerl et al., 2020; Iwata et al., 2016; Kidokoro et al., 2014; Park et al., 2014; Tich et al., 2009; Tich et al., 2011; Tutunji et al., 2018; Walsh, Doyle, Anderson, Lee, & Cheong, 2014). To our knowledge, only one study tested brain metrics with neurodevelopmental outcomes in very preterm infants with no evident brain injury diagnosed with MRI (Hammerl et al., 2020).

Our present study sought to link structural MRI findings at term-equivalent age to neonatal visual performance in very preterm born infants without evident or high-grade brain injury on MRI. Specifically, MRI scores related to the visibility of sagittal strata and the crossroads in vulnerable periventricular areas, consisted of commissural, projection and associative pathways, were correlated to the clinical scores of visual behaviors. Understanding associations between MRI quantitative (brain metrics data) and qualitative features (visibility of transient brain patterns) and visual performance in premature infants will provide insight into developmental mechanisms and may be valuable for predicting altered visual development.

We hypothesized that if we score the level of signal intensity and delineation of surrounding tissue (visibility) of white matter segment II, sagittal strata and periventricular crossroads, especially in the temporal and parietal-occipital lobe, which contain crossing trajectories of visual projections and associative pathways, we will find a possible correlation with visual performance. In addition, temporal crossroad of pathways contain the temporal, or Meyer's loop (Vasung et al., 2010), which guides visual information from subcortical to cortical centers. This temporal loop is commonly known as the anterior portion of the optic radiation. Meyer's loop bypasses from lateral geniculate body into the temporal region before reaching the occipital cortex (Choi, Rubino, Fernandez-Miranda,

Abe, & Rhoton, 2006). This temporal loop is not formed exclusively by optic radiation. Various projection fibers that emerge from the sublentiform portion of the internal capsule participate in this temporal loop and become a part of the sagittal strata Goga and Türe, 2015.

2. Methods

2.1. Participants

Infants were recruited from the neonatal intensive care unit at the University Hospital Centre Zagreb between September 2016 – May 2020. Ninety-one preterm infants, consecutively born between 24^{+0} and 31^{+6} weeks of postmenstrual age (PMA) were eligible. Infants with congenital or chromosomal abnormality, and major brain lesions according to Kidokoro et al. (2013) documented by MRI at term-equivalent age (n = 12) were excluded from the study cohort. The infants who developed retinopathy of prematurity (ROP) > stage 2 (n = 8) during their postnatal course were also excluded from the analysis related to visual function. The final study cohort contained 71 preterm born infants with 38 male and 33 female infants. Clinical details of the infants are described in Table 1.

The traditional 10-rung social ladder MacArthur SSS scale (Adler, Epel, Castellazzo, & Ickovics, 2000) was administered to evaluate socioeconomic status in terms of income, educational level, and occupation. The mean SSS score was 6 (*SD* = 1.5).

Written informed parental consent was obtained for all participants. Ethical approval was obtained from Institutional Review Board of the University of Zagreb, School of Medicine and in accordance with Declaration of Helsinki.

2.2. Assessments

2.2.1. Visual function

At 41^{+5} weeks PMA, infants underwent visual assessment according to the protocol developed by Ricci et al. (2008) that evaluated: (a) ocular movements both spontaneous and in a reaction to a target, (b) ability to fix and follow a target (horizontally, vertically and in an arc), (c) ability to track a colored stimulus, (d) stripes discrimination (evaluated using black and white stripes of increasing spatial frequency from 0.24 to 3.2 cycle/degree) and (e) visual attention at the distance.

According to the protocol, the best performance was defined as: mainly conjugated ocular motility, stable fixation, complete tracking, tracking of colored stimulus, discrimination of a spatial frequency over 2.4 cycles/degree, and visual attention beyond 70 cm.

The assessments of neonatal visual function were scored according to the distribution of frequency of individual items previously collected in a cohort of 109 low risk preterm infants at term age (Ricci et al., 2008). Each item was scored as 0 if the findings fell within the 90th percentile of the reference cohort and 1 if the findings fell outside the 90th percentile. The individual items were summed to compose a global score for the neonatal visual assessment. According to previous data in a reference cohort, 90% of the infants have global scores between 0 and 1 (Ricci et al., 2008). Global scores of 0 and 1 were therefore classified as normal and global scores > 1 as abnormal.

Infants were assessed in a single session (10 min) in a quiet environment with low light. The examination occurred when infants were in an alert behavioral state and a supine position. Responses for each of the nine items were recorded. The examiner (SS) was experienced in neonatal visual function assessment. The examiner avoided talking to the infant while presenting the visual stimuli and kept their face out of the infant's line of vision. The examiner was not aware of the MRI findings.

All infants included in the study had a similar level of care that did not include any specific stimulation of visual or other sensory pathways.

Table 1
Clinical characteristics of study cohort.

Characteristics (n = 40)		Mean (SD) / number (%)
Male sex - *n* (%)		38 (53%)
Gestational age at birth (wk)		27 (1.9)
Birthweight (g)		1087 (328.2)
Small for gestational age - *n* (%)		13 (18%)
Multiple pregnancies - *n* (%)		13 (18%)
Median Apgar score at 5 min		7 (1.7)
Bronchopulmonary dysplasia - *n* (%)		15 (21%)
Sepsis - *n* (%)		17 (24%)
Necrotizing enterocolitis - *n* (%)		16 (23%)
Socioeconomic status (SES)		6 (1.5)
Retinopathy of Prematurity	Grade 0	13 (18%)
	Grade 1	26 (37%)
	Grade 2	32 (45%)
Gestational age at Term MRI (wk)		40.2 (1.4)
Mild abnormality on MRI		42 (59%)
NVA total score	0 – 1	52 (73%)
	2 – 6	19 (27%)

2.2.2. Magnetic resonance imaging examinations and assessment

MRI brain scan was undertaken at 40^{+2} weeks PMA using 3 T MRI scanner (Magnetom Prisma^{FIT}, Siemens; Germany) using 64-channels head/neck coil. Coronal T2-weighted turbo spin-echo sequence (TR/TE = 6000 ms/96 ms, resolution = 512 × 179; voxel size = 0.4 × 0.4 × 1.5 mm), axial T2-weighted turbo spin-echo sequence (TR/TE = 3830 ms/96 ms, resolution = 512 × 256; voxel size = 0.5 × 0.4 × 3 mm) and T1 MPRAGE (eng. high-resolution magnetization-prepared rapid acquisition gradient echo) sagittal sequence (TR/TE=2300/3 ms, resolution=256 ×256, voxel size =1x1x1mm) were used for analysis. MRI scanning was performed after regular feeding. Infants were wrapped/half-fixed within linen diapers and blanket, and a few infants needed sedation (n = ??; phenobarbital 5–10 mg/kg intravenously). MRI scans were analyzed to determine (a) simple brain metrics and (b) the visibility of transient structural patterns.

2.2.2.1. MRI brain metrics. Various brain tissue parameters (Tich et al. 2009, 2011; Walsh et al. 2014; explained in detailed in Table 2, see also Fig. 1) were measured using ITK-SNAP [Software] (version 3.8.0; http://www.itksnap.org/; Yushkevich et al. 2006) and Medixant. RadiAnt DICOM Viewer [Software] (version 2020.1.1 Apr 29, 2020.; https://www.radiantviewer.com). Measurements were performed by two independent raters (AB and IŽI).

Intrarater reliability was analyzed on a sample of 10 randomly selected infants for whom raters repeated all measures. Rater A had ICC values ranging from 0.75 to 0.99, while rater B had ICC values from 0.65 to 0.96. Interrater reliability was also computed using ICC absolute agreement and consistency types. Values of ICC absolute agreement ranged from 0.39 to 0.91, while ICC consistency type coefficients ranged from 0.48 to 0.91. Mean scores from both raters for all brain metrics measurements are presented in Table S1.

2.2.2.2. Visibility of transient structural brain patterns. After exclusion of infants with moderate and severe brain injuries graded by commonly used and generally accepted MRI scoring by Kidokoro et al. (2013), the remaining MRI scans were scored by two independent raters (MR and IŽI) using an additional scoring system developed in our research group, considering visibility of transient structural patterns such as periventricular axonal crossroads and sagittal strata (Judaš et al. 2005; Kostović, & Jovanov-Milošević et al., 2014; Kostović, & Kostović-Srzentić et al., 2014; Žunić Išasegi et al. 2018; Katušić & Raguž et al., 2020; Katušić & Žunić Išasegi et al., 2020; Kostović Srzentić et al. 2020; Milos et al. 2020; see Fig. 2). The visibility of transient structural brain patterns was graded on a 3-point scale as being non-visible (1), poorly visible (2) or fairly visible (3) on MRI. All images were assessed independently by two experienced raters, and who were unaware of the infant's prenatal history.

Interrater reliability was substantial to almost perfect agreement (Kappa coefficient ranged from 0.68 to 0.90). Results of one rater (MR) were randomly selected for further analysis of relationship between transient structural patterns and visual functions.

2.3. Statistical analysis

Data analysis was performed using the SPSS Statistics software package, version 20.0 for Windows (IBM Corporation, Armonk, NY). Interrater reliability of categorical variables was computed using Kappa coefficients, while Intraclass Correlation Coefficients (ICC) were employed for intrarater and interrater reliability analysis of continuous variables. Relationship between outcome variables, clinical variables and measured/scored brain areas was analyzed using different statistical procedures based on types of variables,

Table 2
Structures and neuroanatomical landmarks used in brain metrics method.

Measures			Slice	Neuroanatomical landmark
Tissue measures (mm)				
1	A	Brain bifrontal diameter	cor T2W	Level of olfactory bulbi and olfactory sulci; upper and lower molars
	B	Bone bifrontal diameter	cor T2W	
2	right/left	Frontal lobe height	cor T2W	
3	A	Brain biparietal diameter	cor T2W	Level of the 3rd ventricle, cochlea, basilar truncus apparent
	B	Bone biparietal diameter	cor T2W	
4	A	Brain bioccipital diameter	cor T2W	Level of lateral ventricular atrium
	B	Bone bioccipital diameter	cor T2W	
5	A	Brain fronto-occipital diameter	sag T1W	Midsagittal plane
	B	Bone fronto-occipital diameter	sag T1W	
6	A	Corpus callosum antero-posterior diameter	sag T1W	
	B	Corpus callosum genu height	sag T1W	
	C	Corpus callosum corpus height	sag T1W	
	d	Corpus callosum splenium height	sag T1W	
7	a	Cerebellum transverse diameter	cor T2W	Level of lateral ventricular atrium
	b	Cerebellum vermis height	cor T2W	
8	a right/left	Deep gray nuclei width	axT2W	At the level of foramen of Monroi
	b right/left	Deep gray nuclei height	axT2W	
Cerebrospinalfluid indirect measures (mm)				
9		Interhemispheric distance	cor T2W	Level of the 3rd ventricle, cochlea, basilar truncus apparent
10	right/left	Cranio-caudal interopercular distance	cor T2W	
11		3rd ventricle width	cor T2W	
12	right/left	occipital horns of lateral ventricles width	cor T2W	Level of lateral ventricular atrium

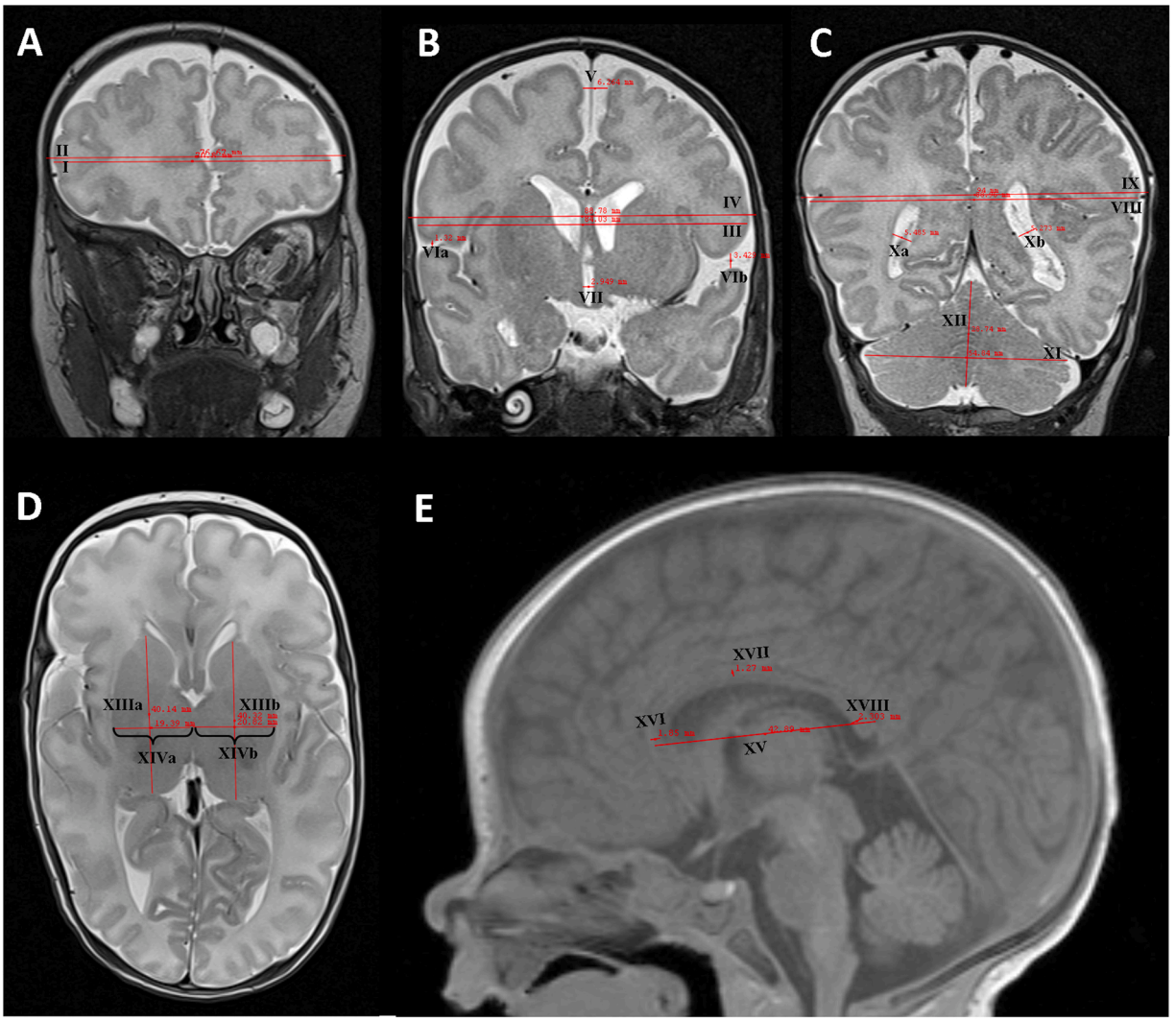

Fig. 1. Overview of brain metrics parameters used on term-equivalent MRI: T2W coronal slices I- brain bifrontal diameter, II- bone bifrontal diameter (A), III- brain biparietal diameter, IV-bone biparietal diameter, V-interhemispheric distance, VIa,b- cranio-caudal interopercular distance, VII- 3rd ventricle width (B), VIII-brain bioccipital diameter, IX-bone bioccipital diameter, Xa,b- occiptial horns of lateral ventricles width, XI-cerebellum transverse diameter, XII- cerebellum vermis height; T2W axial slices- XIIIa,b- deep gray nuclei height, XIVa, b- deep gray nuclei width; T1W sagittal slice- XV- corpus callosum antero-posterior diameter, XVI-corpus callosum genu height, XVII- corpus callosum corpus height, XVIII-corpus callosum splenium height (C).

distribution of continuous variables and whether other assumptions of parametric statistics were met. Pearson's/Point-biserial/Spearman's correlation coefficients were computed among continuous variables. Mann-Whitnney U and Kruskall Wallis tests (with post hoc Dunn's test with Bonfferoni correction) were used, depending on levels of variables, to compute differences in continuous outcome, clinical or measured/scored brain areas between groups. Chi square test or Fisher's exact test were used to examine relationship between categorical variables (depending on whether assumptions for each were met), whereas Goodman and Kruskal's gamma (rank correlation) was used for variables with ordinal quality. A logistic regression analysis explored the potential predictive power of certain brain areas for predicting outcome, i.e., differing preterm infants with deviation or normal Neonatal Visual Assessment total score and Neonatal Visual Assessment subtests score. The statistical significance was set at p (two-tailed) < 0.05.

3. Results

3.1. Study population and patient characteristics

Our sample included 71 participants who were born at a mean of 27^{+1} weeks PMA with a mean birth weight of 1087 g. Using conventional MRI findings, 59% of infants had evidence of mild lesions. The presence and the grade of ROP were noted as follows; 0 for

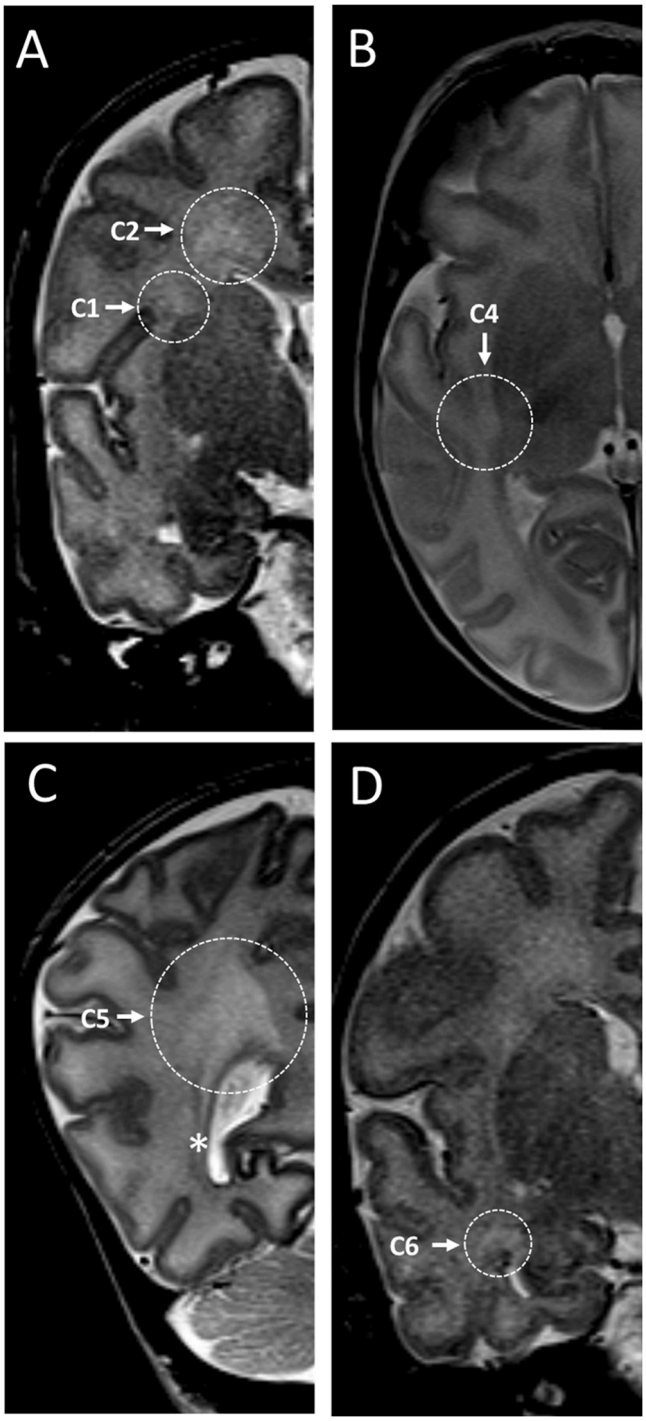

Fig. 2. Qualitative MRI scoring of transient structural patterns at term-equivalent age such as periventricular axonal crossroads C1 and C2 (A), C4 (B), C5 (C) and C6 (D), seen as hyperintense signal on T2W slices. Another component of second white matter segment, sagittal strata, is best seen at this developmental stage as a bilateral hypointense periventricular bands in occipital lobe (marked as * in C).

18,3%, 1 for 36,6% and 2 for 45,1% infants (Table 1).

3.2. Visual assessment scores

Visual assessment scores ranged from 0 to 6. Considering criteria of deviation in function for Neonatal Visual Assessment total

score, there were 19 infants (27%) with abnormal global score. Thirty-three infants scored 0, nineteen scored 1, nine scored 2, six scored 3, one scored 4, one scored 5 and two infants scored 6. We found no significant differences between Neonatal Visual Assessment total score and MRI classification (Mann Whitney $U = 562.00$; $p = 0.557$) and ROP grades (Kruskall Wallis $H = 1.318$; $p = 0.517$).

3.3. Brain metrics, visibility of transient structural patterns and visual functions

Distribution of visibility of temporal crossroad area C6 and frontal and occipital sagittal strata and visual assessment scores are presented in Table 3.

There were no significant relationships between visual outcome expressed by Neonatal Visual Assessment total score and brain metrics variables. In contrast, analyses of relations of specific visual functions and visibility of transient structural patterns revealed a significant correlation between tracking behavior and the visibility of temporal crossroad area C6 (Gamma = - 1.000, p = 0.004). Furthermore, we found a strong correlation between Neonatal Visual Assessment total score and the frontal and occipital sagittal strata (Gamma = - 0.767, $p < 0.001$; Gamma = - 0.965, $p < 0.001$).

When analyzing differences between groups of infants based on visibility of transient structural patterns, significant differences between groups in Neonatal Visual Assessment total scores were obtained for frontal and occipital sagittal strata (Kruskall Wallis H = 12.075, $p = 0.002$; Kruskall Wallis $H = 33.388$, $p < 0.001$ retrospectively) (Fig. 3).

3.4. The predictive power of visibility of transient structural patterns for deviation in visual functions

Based on found correlations between visibility of transient structural patterns and Neonatal Visual Assessment total scores, logistic regression analysis was computed. MRI variables, occipital sagittal strata and temporal crossroad area C6, which showed the highest correlation with visual functions, were selected as possible predictors of categorizing subjects as having abnormal global Neonatal Visual Assessment scores. The model was statistically significant ($\chi^{2(2)} = 29{,}191$; $p < 0001$) and explained 49% of the dependent variable variance (Nagelkerke R2), with 83% correct subject classification. Occipital sagittal strata emerged as a significant predictor indicating that higher visibility of this transient structure decreases the probability of delayed visual functioning in preterm infants (Table 4).

4. Discussion

This study aimed to test if the visual functioning in low-risk very preterm infants at term-equivalent age is related to the volume of brain structures and the visibility of transient fetal brain patterns displayed on MRI. We evaluated visual abilities using a scorable clinical assessment that has been validated previously in neonates at term-equivalent age and related it to brain metrics data and MRI scoring system defined by the visibility of transient fetal structures, namely the visibility of white matter segment II (sagittal strata) and the crossroads in vulnerable periventricular areas.

Applying this structural-functional approach, we have found that visibility of temporal crossroad area C6 and sagittal strata are strongly associated with (a) particular visual functions and (b) Neonatal Visual Assessment global score, relating poor visibility with altered visual functioning. Concerning specific visual functions, wefound that the visibility of temporal crossroads area C6 was strongly related to tracking behavior. Furthermore, the poor visibility of sagittal strata was a strong predictor of overall abnormal visual performance in very preterm infants.

Abnormal Neonatal Visual Assessment total score in our study cohort primarily encompassed impaired smooth pursuit. Thirty-eight percent of the infants (n = 27) showed difficulties in smooth tracking behavior, a finding that is iline with Ricci and colleagues (Ricci et al., 2010). Namely, they demonstrated that even low-risk preterm infants fail at gaze shift test at 3 months corrected age. Although low-risk preterm infants can have a term-equivalent VEP a month or two before term (Taylor, Menzies, MacMillan, & Whyte, 1987), reflecting a rapid maturation likely due to the extended period ex-utero and hence their visual experience (Mercuri, Ricci, & Romeo, 2012; Mirabella, Kjaer, Norcia, Good, & Madan, 2006), they still manifest problems in tracking behavior compared to term-born neonates.

For smooth pursuit, eye movement information is sent to the pontine nuclei and cerebellar cortex via the posterior parietal cortex

Table 3
Distribution of visibility of temporal crossroad area C6 and frontal and occipital sagittal strata (SS) and neonatal visual assessment scores.

Neonatal visual assessment total score	Crossroad C6			Frontal SS			Occipital SS		
	Non visible	Poorly visible	Fairly visible	Non visible	Poorly visible	Fairly visible	Non visible	Poorly visible	Fairly visible
0	1	3	29	4	10	19	0	12	21
1	2	3	14	0	4	15	1	18	0
2	9	0	0	9	0	0	1	8	0
3	6	0	0	6	0	0	3	3	0
4	1	0	0	1	0	0	1	0	0
5	1	0	0	1	0	0	1	0	0
6	2	0	0	2	0	0	2	0	0

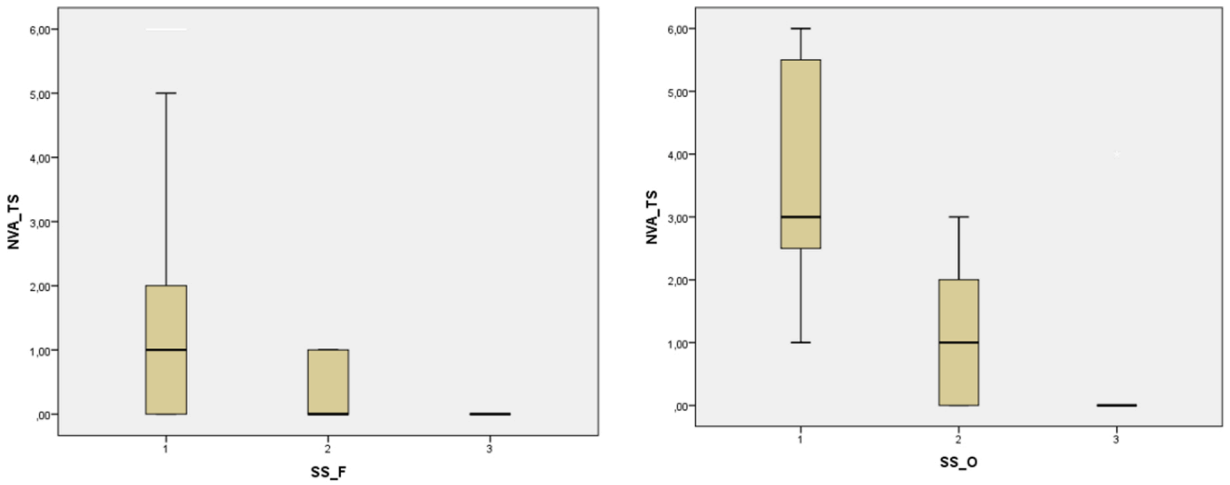

Fig. 3. The comparison of NVA total scores between preterm infants with differential visibility of frontal and occipital sagittal strata. The NVA total scores were significantly higher in the infants with poorly visible sagittal strata than in infants with fairly visible sagittal strata. Bold horizontal lines indicate median values, boxes represent 25th and 75th centiles and whiskers represent range.

Table 4
Predictive power of visibility of occipital sagittal strata (SS) and temporal crossroad area C6 for deviations in neonatal visual functions.

		B	S.E.	Wald	df	*p*	Exp (B)
NVA TS	Occipital SS	-3.116	1.028	9.194	1	0.002	0.044
	C6	-20.869	9080.790	0.000	1	0.998	0.000

and the medial superior temporal visual areas and then onto the motor neurons of the three oculomotor cranial nerves (Leigh & Zee, 1999). Our results indicate the potential role of periventricular crossroad C6 as a neuroanatomical substrate of tracking behavior. This temporal periamygdaloid crossroad area consists of basal forebrain fibers intermingled with fibers of the internal capsule, radiation of the anterior commissure, and the amygdalofugal system (Judaš et al., 2005). Efferent connections from basolateral nuclei of the amygdala are exceptionally widespread to the occipitotemporal network, including the primary visual cortex (V1) (Amaral, Behniea, & Kelly, 2003; Bzdok, Laird, Zilles, Fox, & Eickhoff, 2013; Freese & Amaral, 2006), contributing to the neural framework of the ventral visual pathway. Although the functional consequences of the projections from the amygdala to the occipitotemporal network are poorly understood, these projections are very diffuse (Kravitz, Saleem, Baker, Ungerleider, & Mishkin, 2013), suggesting a role of the amygdala in vision awareness (Duncan & Barrett, 2007; Pessoa, 2010). Furthermore, the basolateral nuclei of the amygdala contain neurons that are visually responsive (Nishijo, Ono, & Nishino, 1988) and broadly selective for the content of the images (Mosher, Zimmerman, & Gothard, 2010), including facial identity and expression (Gothard, Battaglia, Erickson, Spitler, & Amaral, 2007).

We assume that this response characteristic of basolateral neurons in amygdala and its projections to the occipitotemporal network may reflect an association between the visibility of C6 and tracking behavior revealed in the present study. Further support comes from the temporal crossroad that contains Meyer's loop (Vasung et al., 2010). Various projection fibers of the internal capsule, which are the temporopontine fibers, occipitopontine fibers, and the posterior thalamic peduncle (which includes optic radiation), participate in this temporal loop (Goga and Türe, 2015).

Our results showed that good visibility of sagittal strata at term-equivalent age predicted concurrent normal visual functioning in very preterm infants. Sagittal strata are situated at the deep border of the subplate and represent the major gateway of intracerebral trajectory of sensory, motor, and associative pathways (Kostović, & Jovanov-Milošević et al., 2014; Kostović, & Kostović-Srzentić et al., 2014; Vasung et al., 2010; Žunić Išasegi et al., 2018). Sagittal strata are the most prominent in the occipital lobe and encompass geniculocortical fibers (feedforward projections to V1), and pulvinocortical fibers and fibers from basal forebrain (two feedback projections to V1; Pennartz, Dora, Muckli, & Lorteije, 2019), together with associative fibers at the lateral side. Of all associative pathways, the inferior frontooccipital fascicle (iFOF) (Kostović, 1986; Kostović, Judaš, Radoš, & Hrabač, 2002; Vasung et al., 2010; Žunić Išasegi et al., 2018) show the closest association with the sagittal strata, and eventually inferior longitudinal fascicle (ILF) (Catani, Jones, Donato, & Ffytche, 2003), two regions involved in object recognition (Ortibus et al., 2012) and face processing (Taddei, Tettamanti, Zanoni, Cappa, & Battaglia, 2012). These associative fibers gives additional importance to sagittal strata as a complex system of all three types of fiber system - commissural, projection, and associative, which embodies the significance of white matter integrity. Specifically, the typical 'triple' track appearance of sagittal strata at occipital levels on MRI recordings at preterm may be considered a good marker of white matter integrity (Kostović, 2020). Nevertheless, the standard scoring system for evaluating lesions of cortical pathways includes only the posterior limb of the internal capsule (PLIC), which contains only projection pathways. Our results on the early structure-function relationship in the cohort of very preterm infants suggest the importance of sagittal strata as an

additional marker from the neuropathology and neuroradiology point.

The focus of most studies about the visual system in the preterm neonates has been on optic radiation and occipital cortex (Shah et al., 2006; Thompson et al., 2014), and thus did not reflect a general problem of the white matter, whose integrity is generally deficient in preterm neonates (Anjari et al., 2007; Counsell et al., 2006). Neurocognitive studies in preterm children have suggested that a dorsal stream visual system vulnerability is associated with a more significant neural network alteration (Atkinson & Braddick, 2007). The thalamus is a relay structure, potentially linking different cortical functions to dorsal stream visual vulnerability. However, no in-vivo studies have linked thalamocortical connectivity and dorsal stream visual vulnerability in preterm infants. Studies have shown that relatively healthier and lower risk preterms seem to have predominately dorsal stream visual vulnerability compared to infants with more severe brain injury in which both dorsal and ventral stream structures appear to be involved (Geldof, van Wassenaer, de Kieviet, Kok, & Oosterlaan, 2012; Ortibus, De Cock, & Lagae, 2011; Santos, Duret, Mancini, Gire, & Deruelle, 2009). Preterm neonates exhibit signs of cognitive visual dysfunction at term with abnormal fixation shift tests (Ramenghi et al., 2010; Ricci et al., 2008), which is in accordance with our results. Of interest, in our low-risk preterm group, four infants had relatively poor visual functions (visual assessment score above 3), indicating that disturbances to the development of neural systems may not always be apparent on conventional MRI scoring of brain injury, which calls for additional imaging markers with ease of administration in clinical practice. In this context, our findings relating to the visibility of structures on MRI, namely the visibility of white matter segment II (sagittal strata) and the crossroads in vulnerable periventricular areas, suggest these structures could serve as potential complementary parameters in the brain MRI scoring system. Applying these novel neuroimaging markers in clinical practice we might advance not just outcome prediction, but more notably, individually - tailored parental counselling, and clinical decision-making. The latest is particularly relevant in the framework of timely habilitation strategies, while the studies imply the significant effect of early intervention on visual functions in neonatal and early infancy period (Alimović, Katušić, & Mejaški-Bošnjak, 2013; Fiori and Guzzetta, 2015; Fazzi et al., 2021).

Surprisingly, we have not found any association between cerebral and cerebellum volume and visual functions. Our findings are at odds with those of other researchers (Naud, Schmitt, Wirth, & Hascoet, 2017; Shah et al., 2006) who linked cerebral volume with visual behavior. This may reflect the lack of sensitivity for brain volumes as a marker of brain function at certain stages of development and may be better addressed in future studies with an investigation for specific fiber tracts.

Normal visual functions depend on the integrity of a network that includes the eyes, optic nerves, chiasm, and the geniculostriate pathways which include the lateral geniculate body, optic radiations and primary visual cortices. The visual information is then relayed to association cortices, which are responsible for interpreting meaning, detecting movement, locating an object in space, or controlling a response. The cortical regions involved in higher-order visual processing include the frontal, parietal, and inferior temporal lobes (McIntosh & Schenk, 2009). Understanding the relations between brain structure and visual function is especially relevant given the impact that early visual function can have on cognitive development (Ramenghi et al., 2010; Ricci et al., 2011). As a consequence, subtle difficulties in visual perception, seen in very preterm infants, can manifest and interfere with their neurodevelopmental outcome (Anderson & Doyle, 2008; Braddick & Atkinson, 2011; Delobel-Ayoub et al., 2009; Mulder, Pitchford, Hagger, & Marlow, 2009).

The main limitation of this study could be found in applying simple brain metrics methods instead of more sophisticated computational morphometric volumetric techniques. Nevertheless, brain metrics has good comparability with brain volumes obtained with different volumetric techniques (Tich et al., 2009). Furthermore, it showed high intra- and interrater consistencies in the present study, which makes it a reliable reproducible MRI quantitative method with easy administration in clinical practice.

5. Conclusions

Impaired visual development is common following very preterm birth, even in low-risk preterm infants. Demonstration of association between the fetal pattern of transient visibility of sagittal strata and maturation-dependent visibility of temporal crossroad area C6 with visual performance in very preterm infants at term-equivalent age, suggests that the integrity of growing projections and associative pathways at crossing points is essential for development of early visual functions. Our findings support implementing these additional neuroimaging markers to the conventional MRI scoring system, which may provide us with a complete understanding of the inter-relationship between structural connectivity and visual function in the neonatal period.

CRediT authorship contribution statement

Katušić Ana: Conceptualization, Methodology, Writing – original draft, Visualization. **Žunić Išasegi Iris:** Investigation, Visualization, Writing – review & editing. **Predrijevac Nina:** Formal analysis, Visualization. **Raguž Marina:** Investigation, Validation. **Ćaleta Tomislav:** Resources, Investigation. **Seitz Snježana:** Investigation, Resources. **Blažević Andrea:** Investigation, Validation. **Radoš Milan:** Investigation, Resources, Visualization. **Kostović Ivica:** Writing – review & editing, Supervision.

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Declaration of interest

None.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.infbeh.2022.101697.

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