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Original Article

Specific cognitive deficits in preschool age correlated with qualitative and quantitative MRI parameters in prematurely born children

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Key Words
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preschool age

Background: Cognitive deficits after perinatal brain lesion in preterm infants are among the most common neurodevelopmental disturbances. The relationship between structural changes on at term magnetic resonance imaging (MRI) and cognitive deficits in the preschool age should be a special focus due to timely intervention. The aim of this study was to correlate qualitative and quantitative MRI parameters of perinatal brain lesion in preterm children, on early neonatal MRI and follow up MRI, with general and specific cognitive functions in the preschool age.

Methods: Twenty-one preterm infants with verified perinatal lesions based on clinical and ultrasound data underwent a brain MRI at term-equivalent age and a second MRI between 3 and 5 years of age. Qualitative and quantitative MRI analyses were done. All subjects underwent cognitive assessment (3—5 years) using *Wechsler Preschool and Primary Scale of Intelligence (WPPSI-III)* and *Developmental Neuropsychological Assessment (NEPSY-II)*.

Results: Results show that many structural changes on at term MRI and on follow up MRI in preterm born children moderately correlate with specific cognitive deficits in preschool age. At term equivalent MRI, white matter changes and cortical thickness correlate to general and specific cognitive functions in infants born preterm. By analyzing follow up MRI at preschool age, structural changes of different white matter segments, corpus callosum, cortical thickness and lobe volume correlate to some specific cognitive functions.

Conclusion: Besides general cognitive delay, specific cognitive deficits in preterm children should be targeted in research and intervention, optimally combined with MRI scanning,

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providing timely and early intervention of cognitive deficits after perinatal brain lesion. Our results, as well as previously published results, suggest the importance of detailed preschool neuropsychological assessment, prior to enrolment in the school system. Although preliminary, our results expand our understanding of the relationship between early brain developmental lesions and cognitive outcome following premature birth.

1. Introduction

Continuous quality improvement in neonatal care has resulted in increased survival rate of very preterm infants and has led to a decrease in major neurodevelopmental pathology. However, the relationship between structural brain lesions and a specific cognitive outcome remains a challenge and requires further investigation.[1–9] Studies show that cognitive deficits after perinatal brain lesion in preterm infants are a common neurodevelopmental disturbance, even more common than motor and sensory deficits.[4,8,10] There is a growing interest in "subtle" cognitive deficits of children without major disabilities.[11] The relationship between magnetic resonance imaging (MRI) and later cognitive outcome provides an objective and scientific insight into the neuropathological and vulnerability frame for neurodevelopmental deficits and is important for clinicians who work with preterm infants and their families. One of the most challenging problems is the prediction of long-term outcome after mild or moderate injury.[12] Today, the focus of investigation is mostly on finding early neonatal markers of later cognitive deficits, which will help in identifying children who are at risk of neurodevelopmental impairments and may benefit from early intervention. In reviewing research dealing with the relationship between cognition and MRI changes, there are a few facts that should be pointed out. There is a reliance on a single global outcome measure, such as developmental or intelligence quotient, as the only indicator of cognitive outcome in several studies. Cognition is a complex range of processes, broader than the general ability usually measured by developmental or intelligence quotients. This quotient is not a criterion in assessing the cognitive consequences of perinatal lesion in preterm infants, especially due to the fact that there is a substantial number of children with mild cognitive impairment.[12,13] In addition to evidence of global intellectual delay in children with more severe lesions, children with perinatal injury may have specific deficits in numerous areas: visuo-motor integration, visuo-spatial processing, verbal and language functions, learning, memory, executive functions and attention.[13–16] So far, efforts to identify early markers have been disappointing as perinatal risk factors (such as low birth weight, small gestational age or prolonged ventilation), only slightly correlating with a later cognitive impairment. The brain MRI may not only help pinpoint the lesion and its nature, but it can also provide possible prognostic information. Recent advances in neuroradiology and neonatology provide the opportunity of obtaining an MRI scan in the preterm infant at term equivalent age (TEA).[4,17–19] The main neuropathological cornerstone of long-term neurodevelopment in preterm children is a lesion of cerebral white matter (WM).[4,18,20,21] Although many MRI changes have been described, such as WM volume reduction and ventricular dilatation, thinning of the corpus callosum (CC) and delayed myelination, as well as MRI diffuse excessive high signal intensity (DEHSI) of cerebral WM abnormalities, it is not yet clear whether these findings represent a structural or pathological cornerstone.[4,22,23] Developmental vulnerability of WM is related to long cortico-cortical associative pathways especially important in cognition.[8] Considering MRI volumetry, a meta-analysis provided by de Kieviet et al. showed that, in very preterm and very low-birthweight children and adolescents, decreased volume of WM, grey matter (GM), cerebellum, hippocampus and CC were associated with lower IQ, impaired executive functioning and overall diminishment of many other brain functions.[24] There is a modest number of studies with TEA MRI together with follow up of cognitive outcome after 2 years.[7,25–27] Many cognitive functions have extended developmental trajectories, so specific cognitive deficits should be assessed after 3 years, but before school age, as they can predict later learning difficulties in schooling.[13] Finally, there is notable variability in the measurement of brain pathology. Volumetric MRI analysis is time-consuming and requires advanced image processing. Furthermore, interpretation of TEA MRI data requires well-trained experts in developmental or pediatric neuroradiology. Although there are many volumetric studies in childhood and adolescence in relation to cognitive outcome, the relationships between volumetric TEA brain measures of preterm infant and cognition are less frequent.[24,27]

We propose that preterm infants with a structurally defined perinatal brain lesion will have specific cognitive deficits in several domains. It is also assumed that detailed qualitative and quantitative TEA MRI measures will correlate with cognition in the preschool age.

The goals of this study were to examine whether preterm infants with a structurally defined perinatal lesion, apart from general intellectual disability, have specific cognitive deficits in the preschool age and also to relate qualitative and quantitative MRI abnormalities of perinatal brain lesion (TEA MRI and follow up MRI) with general and specific cognitive functions in the preschool age.

2. Methods

2.1. Subjects

This study included 21 prematurely born infants, at an average age of 28 gestational weeks, admitted to the Neonatal Intensive Care Unit (NICU), University Hospital Centre Zagreb (Supplementary Table 1). All subjects had periventricular lesion, revealed using ultrasound, and underwent neonatal TEA MRI. At preschool age (3–5 years), follow-up MRI and neuropsychological testing were conducted. Infants with chromosomal or congenital abnormalities, metabolic disease, hydrocephalus and massive infarctions, which can potentially affect neurodevelopmental outcome, were excluded. Background and clinical characteristics of subjects included in the study are presented in Supplementary Table 1. This study is prospectively designed and is part of a large project at the Croatian Institute for Brain Research. Informed parental consents were obtained at the beginning of research from parents during hospitalization of their child in NICU. All parents agreed to participate in the study (none refused). Ethical approval was obtained from Institutional Review Board of the University of Zagreb, School of Medicine.

2.2. Procedure for MRI

2.2.1. MRI acquisition

MRI scans were obtained on 3T MRI scanner (Magentom Trio, Siemens). MRI was done twice; a first TEA MRI, between 35 and 54 gestational weeks (average 41), and a second MRI when children were between 3 and 5 years. The following sequences were used: SE T1 (sagittal, 5 mm), FSE T2 axial (5 mm), PD T2 coronal (5 mm) and GRE 3D axial (1.1 mm), as well as high-resolution 3D T1 MPRAGE sequence in the sagittal plane with the recording parameters: TR/TE = 2300 ms/3 ms, tilting angle = 9°, matrix size = 256 × 256, size voxel = 1 × 1x1mm, used for volumetry.

2.2.2. Qualitative MRI scoring

An expert developmental neuroradiologist graded structural changes using scoring systems. The basic scoring system included the following variables in all lobes separately: lateral ventricles dilatation, changes in signal intensity and reduction of WM. An extended scoring system included WM segments, crossroads, visibility of sagittal strata and border with subplate, deep GM and cerebellar abnormality, with pathomorphological changes such as cysts, hemorrhage and focal signal abnormalities and ventricular dilation (Fig. 1).[8,28–30] Parameters in both scoring systems were graded as normal, mild, moderate and severe. Maturation assessment included myelination of the posterior limb of the internal capsule and ventrolateral thalamus. The extended scoring system also included the visibility of transient fetal compartments and WM segments for subplate remnant, sagittal strata, periventricular crossroads and WM segments borders.[17,28]

2.2.3. Quantitative volumetric methods

We used the MNI Toolbox program (http://www.bic.mni.mcgill.ca/ServicesSoftware/MINC), developed and calibrated at the Montreal Neurological Institute, McGill University, Montreal, Canada. It is used for the analysis of high resolution MPRAGE images and tissue segmentation based on the intensity differences in-between voxels. Primary segmentation and classification of the voxels of tissue according to their intensities was conducted using artificial neural network algorithm. Regional segmentation of lobe surface (frontal, parietal, temporal, occipital, insular, limbic) was also conducted. We calculated the volume, thickness and gyrification index. CC was quantitatively measured; manual delineation was obtained using the Analyze 7.0 (Mayo Clinic, USA) software.

2.3. Neurocognitive assessment

Children underwent a comprehensive assessment of general and specific cognitive abilities at the age of 3–5 years over two sessions. The psychologist was unaware of the MRI data and child development but not blinded to the cohort group. The Wechsler Preschool and Primary Scale of Intelligence (WPPSI-III) was applied estimating the Full-Scale intelligence quotient (IQ), Verbal IQ (VIQ) and Performance IQ (PIQ). Developmental Neuropsychological Assessment (NEPSY-II) was used to assess specific cognitive functions: executive functioning (*Statue*), language (*Comprehension of instructions*, *Speeded naming*), memory (*Narrative memory*), sensorimotor (*Visuo-motor precision*) and visuo-spatial processing (*Geometric puzzles*, *Design copying*).

2.4. Statistical analysis

Data analysis was performed using the SPSS 22.0, Statistical Package for Social Sciences (Chicago, Illinois, Inc.). Correlation coefficients were calculated between MRI and cognitive variables: Spearman rank coefficient for qualitative MRI variables (ordinal scale), Pearson correlation for quantitative variables TEA MRI, and partial correlations when controlling for age of assessment at follow up MRI (because it was not conducted at exactly the same age for all subjects). Values of $p < 0.05$ were considered statistically significant.

3. Results

3.1. Cognitive functions at preschool age

According to the WPPSI-III, the normal group mean is 100 (SD = 15). In our sample, the average IQ was in the low average intelligence level (M = 88.1, SD = 16.29, range 48–124), VIQ at average (M = 90.3, SD = 14.80, range 52–131) and PIQ was in the low average level (M = 89.6, SD = 15.21, range 60–111). Three children had extremely low IQ (<70) and two were borderline level (70–79). Therefore, one-fourth of the sample had some level of intellectual disability. Five children had IQ in the low average level, ten were at average level and one had superior IQ.

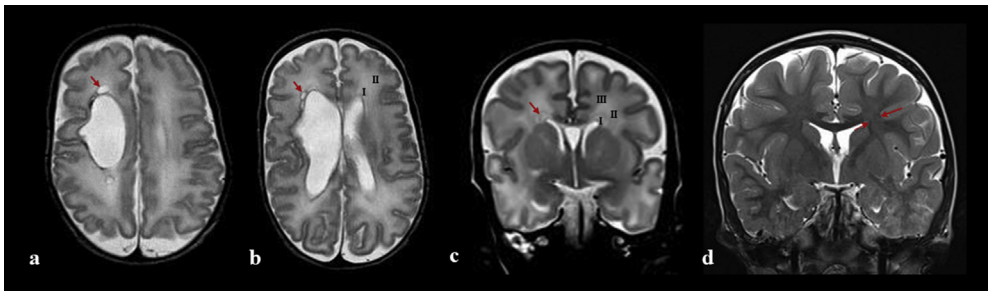

Figure 1 (Four figures a—d). The most common MRI visible pathologies scored by basic and extended scoring systems as illustrative case images for mild, moderate and severe structural changes. Mild structural changes are presented as changes of intensity (red arrow) in the frontal crossroad (C1) in the right hemisphere at TEA MRI, coronal T2 image (c) and dilatation of the lateral ventricles with WM thinning in the left hemisphere (between red arrows) at follow up MRI, coronal T2 image (d). Moderate structural changes are presented as dilatation of lateral ventricle on the left hemisphere at TEA MRI, axial T2 image. Severe structural changes are presented as dilatation of lateral ventricle on the right hemisphere, as well as loss of periventricular WM, more pronounced on the right side at TEA MRI (b). In addition, pathomorphological changes in the form of cysts (red arrow), are visible in the C1 crossroad located in the right frontal lobe (a, b). WM segments I and II are presented in the left hemisphere at TEA MRI, axial T2 image (b), while WM segments I, II and III are presented in the left hemisphere at TEA MRI, coronal T2 image (c).

On the NEPSY-II, a result of 7 or below is considered as a deficit. Cognitive deficits in narrative memory, executive functions, comprehension and speeded naming were found (Fig. 2). The lowest average result was on Geometric puzzles, implying a merge deficit in visuospatial processing. Visuo-motor precision and Design copying were in the normal lower range.

3.2. Qualitative and quantitative MRI measurements and general and specific cognitive functions

3.2.1. Correlation between TEA MRI and cognitive functions

Correlations were calculated between qualitative and quantitative measurements of the TEA MRI and all IQ scores and specific functions. Because of the great number of parameters, only significant correlations are presented in Table 1.

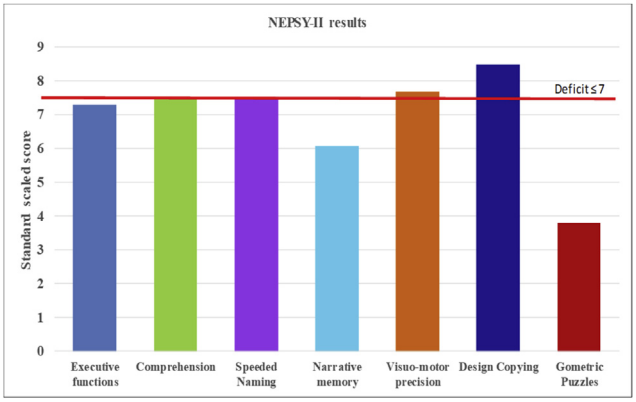

Figure 2 Results of specific cognitive functions on NEPSY-II subtests in a sample of high-risk preterm preschool-aged children. Note: the result on the Geometric Puzzles subtest was converted from percentile rank to a standard scale score for the purpose of comparison with results on other subtests expressed in standard scores.

WM reduction in the parietal and occipital lobes was related to IQ scores. Ventricular enlargement (frontal and occipital) was negatively related to IQ scores. Considering volumetry, cortical thickness showed positive correlation with IQ scores in frontal, occipital, parietal and limbic lobes. Cerebrospinal volume was negatively related to IQ and PIQ. Insular volume was positively related to PIQ.

Significant correlations were found between specific cognitive functions and qualitative measures (Table 1). WM reduction in the parietal, temporal and occipital lobes was related to executive functions, language, visuo-motor and visuo-spatial tasks. Ventricular enlargement in the frontal, temporal and occipital lobes related to most cognitive functions as well as sagittal strata.[8,29]

Many volumetric measures were also related to NEPSY-II. Cortical thickness in the frontal lobe was related to specific cognitive functions. A positive correlation was found between thickness of the parietal, temporal, occipital, limbic and insular lobes and narrative memory, visuo-spatial and visuo-motor functions. Cerebrospinal fluid volume was negatively related to visuo-motor precision. Insular volume was positively related to visuo-spatial tasks. Other measurements at TEA MRI were not related to cognitive scores.

3.2.2. Correlation between follow up MRI and cognitive functions

Considering qualitative MRI measures, WM reduction in the parietal and occipital lobes were negatively related to all IQ scores. Frontal WM reduction related only to PIQ (Table 2). Occipital volume was negatively related to IQ. WM reduction in the frontal, parietal and occipital lobes was negatively related to executive, language and visuo-spatial tasks. CC measured in the preschool age related to PIQ and visuo-motor precision.

In contrast to TEA MRI, where positive correlations between thickness and cognition were found, thickness in the occipital, temporal lobes and insula in the preschool age was negatively related to comprehension and visuo-spatial

Table 1 Correlations between qualitative and quantitative measurements at TEA MRI and IQ scores (WPPSI-III) and specific cognitive functions on the NEPSY-II at preschool age. Correlations significant at the 0.05 level are marked with *, and correlations significant at the 0.01 level are marked with **.

MRI	WPPSI-III			NEPSY-II specific cognitive functions						
	IQ	VIQ	PIQ	ST[a]	CI[b]	SN[c]	NM[d]	VMP[e]	DC[f]	GP[g]
Qualitative										
Extended scoring system[8,28,30]										
Subplate border toward cortex — F[h]				−.60*		−.60*				
Subplate border toward cortex — O[i]				−.60*		−.60*				
Sagittal strata — F									−.50*	−.70**
Sagittal strata — O									−.50*	−.70**
VENTR F	−.54*	−.51*	−.55*	−.54*	−.64**			−.52*	−.60**	−.49*
VENTR T[j]					−.53			−.50*	−.50*	
VENTR O	−.43*		−.52*		−.51		−.54		−.53	
Basic scoring system										
WM reduction P[k]	−.50*	−.48*	−.51*		−.67**	−.66**			−.52*	−.51*
WM reduction T					−.53*			−.50*	−.48*	
WM reduction O	−.48*	−.49*	−.49*	−.60*	−.47*				−.48*	−.49*
Quantitative (volumetry)										
Thickness F	.45*	.40*	.47*	.51*	.42*		.55*			.46*
Thickness O	.42*		.46*				.53*			
Thickness T				.53*			.58*			.46*
Thickness P	.45*		.49*	.52*			.46*	.43*		
Thickness Insula				.52*			.62*			.43*
Thickness limbic lobe			.39*				.52*	.40*		
Volume Insula			.40*						.44*	.55*
CSFV[l]	−.49*		−.55**					−.48*		

[a] ST-Statue (executive functions).
[b] CI-Comprehension of instructions.
[c] SN-Speeded naming.
[d] NM-Narrative memory.
[e] VMP-Visuo-motor precision.
[f] DC-Design copying.
[g] GP-Geometric puzzles.
[h] F — frontal.
[i] O-occipital.
[j] T-temporal.
[k] P-parietal.
[l] CSFV — cerebrospinal fluid.

tasks (Table 2). Total, frontal, occipital and limbic volumes were negatively related to several cognitive functions.

4. Discussion

In this study, we found that prematurely born children with identified structural abnormalities showed specific cognitive deficits in the preschool age in several domains (visuospatial processing, memory, executive functions and language). Average IQ of the sample was below the expected level and one quarter of the sample had a general intellectual disability. Together with previous evidence, our findings suggest that IQ, as the only indicator of outcome, is not enough in assessing the cognitive consequences of perinatal brain lesion in preterm infants.[14–16] This is consistent with many studies referred to previously, regarding the deficits in several cognitive domains exhibited by preterm children with perinatal lesion across childhood and adolescence.[4,10,11,21,28] The finding of specific cognitive deficits in children with mild and moderate MRI identified lesions is of particular interest since large-scale perinatal studies did not reveal this type of finding.[15] The most significant abnormalities seen in telencephalic WM also showed significant specific cognitive correlates. Cortical thickness, as a measure of cortical abnormality, showed moderate correlations. Consistent with previous studies, the possible structural substrate was in WM lesion.[4,21] We discuss bellow the relationship between qualitative changes of WM segments with specific cognitive deficits and the relationship between quantitative volumetric changes and specific cognitive functions.[8,28,31] We also argue that specific cognitive functions in preterm children should be assessed in the preschool age for the purposes of timely intervention.

Table 2 Correlation between qualitative and quantitative measurements (when controlling for age of assessment) of follow up MRI with IQ scores (WPPSI-III) and specific cognitive functions on the NEPSY-II at preschool age. Correlations significant at the 0.05 level are marked with *, and correlations significant at the 0.01 level are marked with **.

Follow up MRI	WPPSI-III			NEPSY-II specific cognitive functions						
	IQ	VIQ	PIQ	ST[a]	CI[b]	SN[c]	NM[d]	VMP[e]	DC[f]	GP[g]
Qualitative										
WM reduction F[h]			−.45*	−.46*	−.47*				−.59**	
WM reduction P[i]	−.37*	−.38*	−.47*	−.49*	−.50*				−.60**	−.44*
WM reduction O[j]	−.58**	−.49**	−.65**	−.52*	−.64*			−.51**	−.67**	−.48*
Quantitative (volumetry)										
Controlled for: age										
Callosum surface			.50*					.49**		
Thickness O					−.65**					
Thickness T[k]					−.53*					−.54*
Thickness Insula										−.52*
Volume F							−.57*			
Volume O	−.57*	−.50*	−.55*	−.58*		−.55*			−.50*	−.57*
Volume limbic lobe										−.54*
Volume Total				−.57*			−.60*			

[a] ST - Statue (executive functions).
[b] CI-Comprehension of instructions.
[c] SN-Speeded naming.
[d] NM-Narrative memory.
[e] VMP-Visuo-motor precision.
[f] DC-Design copying.
[g] GP-Geometric puzzles.
[h] F — frontal.
[i] P-parietal.
[j] O-occipital.
[k] T-temporal.

4.1. Relationship between qualitative MRI measures and cognitive functions

Semiquantitative data on TEA MRI scoring have shown that the major abnormalities are related to WM and its segments, as defined in our previous studies.[8,28,31] The WM abnormalities are known as the most consistent finding in preterm infants with prospective hypoxic-ischemic lesion.[3,4,10,17,21,22,29] The reduction of WM volume is probably caused by a reduction of different WM segments, namely crossroads, sagittal strata and centrum semiovale.[8,17,28] This is the most consistent finding demonstrating a significant correlation with outcome. Sagittal strata contain sensory projections and associative pathways and their changes in occipital, parietal and temporal lobes may partially explain the specific cognitive deficits found using NEPSY-II. Volume changes in another portion of WM segments, periventricular crossroads, which are an important sign of periventricular growth of pathways in the fetal and early preterm brain, seem to be a less reliable qualitative indicator at term and do not show abnormalities in signal intensity in the preschool age. However, at term their presence may be an indicator of "normal" development.[17] It is very likely that crossroads in the frontal lobe show a different pattern of maturation, which may partly explain the inconsistency of our findings when compared with the findings of Kidokoro et al.[17]

4.2. Relationship between quantitative MRI measures and cognitive functions

In general, quantitative volumetric measurements at TEA MRI were related to cognition at preschool age, demonstrating that widely used volumetric measurements in preterm infants may indeed be used in extended diagnostic follow up for this vulnerable group.[25,26] However, interpretations should be taken with caution, since the values of volumetric measurements were claimed to be below term infant values, even in normotypic developing preterms.[1–8]

The most accessible WM structure for measurements is the CC, a major commissural pathway that belongs to segment I of the periventricular WM and forms the roof and walls of the lateral ventricles, running through the subventricular fiber-rich zone and extending as a component of sagittal strata in the occipital lobe.[28,31] Thus, the fibers of the CC can be damaged at several crucial topographical points in the periventricular area, in the main body and in the extension in the sagittal strata. This vulnerable topographical position may explain the positive correlation of the CC area in the preschool age with PIQ and the visuomotor precision task.[8] The importance of the CC for cognitive processing, especially nonverbal, is consistent with other studies with children and adolescents who were born preterm, healthy children and adolescents and

healthy adults.[30,32,33] The finding that the CC area in TEA is not related to cognition in the preschool age may be explained by structural plasticity, which is characteristic of an immature, developing brain.[34] In the case of the CC, one should consider that the CC shows an exuberant growth pattern and has relatively late myelination.[35] A lesion in preterm infants can alter this normally occurring reorganization of callosal connections.

A special problem in the interpretation of cognitive deficits is a prospective lesion of the enigmatic subplate zone.[10,21,28,36] The subplate zone may be defined as a synapse-rich, extracellular matrix-rich compartment containing waiting afferent axons and neurons with advanced differentiation.[28,37] The delineation of this zone in the preterm infant is easy, but at term age it is reduced on the subplate remnant situated between gyral WM and cortical layer VI.[28] The subplate is probably affected with the most superficial portion of WM in a pathological condition called diffuse periventricular leukomalacia and is a prospective candidate as a substrate for cognitive deficits in children born prematurely.[8,10,21,36,37]

The quantitatively analyzed cortical thickness in the frontal, temporal, occipital, parietal, insular and limbic lobes is another recommended MRI variable with prospective significance for predicting cognitive outcomes.[38] Our finding that cortical thickness in preschool MRI negatively correlates with some specific cognitive tasks, in contrast to the positive correlations with TEA MRI, is very interesting because it incorporates cortical layers into the picture of WM abnormalities in the preterm infant. This is consistent with the study of Sølsnes et al., who found a negative relationship between cortical thickness and IQ in a group of very low birth weight children and a control group.[39] Other similar studies in normally developing children also show that cortical thinning was correlated with improved cognitive functioning.[38,39] However, there is evidence that thickness of some regions shows positive association with IQ.[39]

Severe perinatal injuries to the developing preterm brain can lead to extensive plastic changes to compensate for the injury-related cell loss, which is reflected in greater volume. However, newly generated neurons and synapses may cause alterations in synaptic pruning to produce functional connections after hypoxic-ischemic lesion. Studies demonstrated inverse correlations between MRI parameters such as ventricular volumes, cortical GM volume and cognitive functions with volumes at TEA and ages between 2 and 5.5 years.[30,38] In contrast to other studies, we did not find a relationship between WM and GM volume and cognitive functions.[30,39] The finding of enlarged ventricles related to reduction of WM has already been described by several authors.[26,40] Once again, ventricular enlargement was demonstrated to be a reliable indicator of WM deficit, showing a correlation with specific cognitive functions. Although brain development continues into young adulthood and cognitive functions and IQ can change over time and could be prompt by experience, studies show that very preterm individuals more often suffer from cognitive problems and these problems are relatively stable from infancy into adulthood.[41,42] Our results, together with previously published results of other groups, suggest the importance of detailed preschool neuropsychological assessment prior to enrolment in the school system. Apart from general intellectual delay, specific cognitive deficits in preterm children should be targeted in research and intervention, providing timely and early intervention for cognitive deficits following perinatal brain lesion.

Although preliminary, our results with a sample of prematurely born infants expand our understanding of the relationship between early brain growth and cognitive outcome following premature birth. Future studies, using advanced MRI techniques such as diffusion tensor imaging, MRI spectroscopy and functional MRI, are needed to explore how specific pathways and time of lesion onset are related to cognitive and/or motor and sensory deficits.

Conflicts of interest

The authors have no conflicts of interest relevant to this article.

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Appendix A. Supplementary data

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