Cerebral perfusion differences are linked to executive function performance in very preterm-born children and adolescents

Hijman, Anna-Isabella S ; Wehrle, Flavia M ; Latal, Beatrice ; Hagmann, Cornelia F ; O'Gorman, Ruth L

DOI: https://doi.org/10.1016/j.neuroimage.2023.120500

NeuroImage 285 (2024) 120500

Contents lists available at ScienceDirect

NeuroImage

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

Cerebral perfusion differences are linked to executive function performance in very preterm-born children and adolescents

Anna-Isabella S. Hijman [a], Flavia M. Wehrle [b,c,d], Beatrice Latal [c,d], Cornelia F. Hagmann [b,d], Ruth L. O'Gorman [a,d,e,*]

[a] Center for MR Research, University Children's Hospital Zürich, Zürich, Switzerland
[b] Department of Neonatology, University Hospital Zürich, Zürich, Switzerland
[c] Child Development Center, University Children's Hospital Zürich, Zürich, Switzerland
[d] Children's Research Center, University Children's Hospital Zürich, Zürich, Switzerland
[e] Zürich Center for Integrative Human Physiology, University of Zürich, Zürich, Switzerland

ARTICLE INFO

Keywords:
Cerebral blood flow
MRI
Preterm
Executive functions

ABSTRACT

Children and adolescents born very preterm are at risk of cognitive impairment, particularly affecting executive functions. To date, the neural correlates of these cognitive differences are not yet fully understood, although converging evidence points to a pattern of structural and functional brain alterations, including reduced brain volumes, altered connectivity, and altered brain activation patterns. In very preterm neonates, alterations in brain perfusion have also been reported, but the extent to which these perfusion alterations persist into later childhood is not yet known. This study evaluated global and regional brain perfusion, measured with arterial spin labelling (ASL) MRI, in 26 very preterm children and adolescents and 34 term-born peers. Perfusion was compared between groups and relative to executive function (EF) scores, derived from an extensive EF battery assessing working memory, cognitive flexibility, and planning. Very preterm children and adolescents showed regions of altered perfusion, some of which were also related to EF scores. Most of these regions were located in the right hemisphere and included regions like the thalamus and hippocampus, which are known to play a role in executive functioning and can be affected by prematurity. In addition, perfusion decreased with age during adolescence and showed a significant interaction between birth status and sex, such that very preterm girls showed lower perfusion than term-born girls, but this trend was not seen in boys. Taken together, our results indicate a regionally altered perfusion in very preterm children and adolescents, with age and sex related changes during adolescence.

1. Introduction

Worldwide, approximately 15 million infants are born prematurely every year, which means they are born before 37 completed weeks of gestation according to the WHO definition of preterm birth. (Blencowe MRCPCH et al., 2012; Purisch and Gyamfi-Bannerman, 2017) In Switzerland, approximately 6 % of infants are born preterm and 1 % are born very preterm (VPT), that is before 32 weeks of gestation (European Perinatal Health Report, 2023). With advances in neonatal ICU care, survival rates even amongst the extremely preterm infants have increased (Vogel et al., 2018). However, very preterm born infants remain at risk for perinatal and postnatal complications of immaturity. More specifically, there is a direct correlation between the degree of prematurity and the likelihood for the infants to experience encephalopathy of prematurity with cystic and diffuse periventricular leukomalacia (PVL), neuronal/axonal disease, germinal matrix hemorrhage-interventricular hemorrhage (GMH-IVH) (Volpe, 2009) and cerebellar haemorrhage, which may lead to major neurodevelopmental disabilities such as cerebral palsy, severe cognitive impairments, and behavioral problems such as autism spectrum disorder

Abbreviations: ASL, arterial spin labeling; CBF, cerebral blood flow; EF, executive functions; IES, intra-/extra-dimensional shift task; RWT, Regensburger wortflüssigkeits-test; SOC, stockings of Cambridge; SWM, spatial working memory task; TEA, term equivalent age; TB, term-born; VPT, very preterm; WBP, whole brain perfusion.

* Corresponding author at: Center for MR Research, University Children's Hospital Zürich, Zürich, Switzerland.
E-mail address: ruth.tuura@kispi.uzh.ch (R.L. O'Gorman).

https://doi.org/10.1016/j.neuroimage.2023.120500
Received 12 July 2023; Received in revised form 8 December 2023; Accepted 12 December 2023
Available online 20 December 2023

(Schlapbach et al., 2012). However, studies have shown that even in the absence of major brain lesions, and motor or cognitive disabilities, many children and adolescents born very preterm still experience behavioral, social and academic problems (Wehrle et al., 2016; Bhutta et al., 2002). Specific deficits in EF like planning, working memory, inhibition, and cognitive flexibility seem to be more prevalent in VPT-born than term-born (TB) children (Mulder et al., 2009; Aarnoudse-Moens et al., 2009; Stålnacke et al., 2019). Considerable research attention has been devoted to define some of the anatomical and developmental correlates of these executive function deficits, including research on reduced brain volume (Taylor et al., 2011; Nosarti et al., 2014) and cortical thickness (Skranes et al., 2012), altered thalamocortical connectivity (Ball et al., 2013; Wehrle et al., 2020) and white matter microstructure (Vollmer et al., 2017), as well as functional alterations like altered metabolism (Schnider et al., 2020a) and neuronal activation patterns in executive function networks (Nosarti et al., 2006).

To fully investigate the neurobiological mechanisms following very preterm birth, various imaging modalities have been employed. Conventional magnetic resonance imaging (MRI) and ultrasound (US) techniques are utilized to identify major brain lesions, and studies using quantitative MRI techniques have contributed to the generation of more objective and reproducible measurements of brain growth and development in VPT children (Counsell and Boardman, 2005). However, even in the absence of overt structural abnormalities, preterm birth appears to disrupt brain development in a number of ways. Individuals born prematurely have reduced cerebral volumes in childhood and adolescence (Ment and Vohr, 2008), but different regions of the developing preterm brain appear to have varying degrees of vulnerability. Specifically, frontotemporal, basal ganglia, cerebellar, and hippocampal regions appear to be particularly affected (Peterson et al., 2000).

In particular, studies using diffusion tensor imaging (DTI) have identified differences in the development of white matter in preterm infants compared to term-born (TB) infants (Dibble et al., 2021). These differences are detectable even in the absence of anomalies on cranial ultrasound examinations, suggesting a potential delay in the maturation of oligodendrocytes and/or axonal damage. Furthermore, these alterations in white matter structure appear to persist into late childhood and early adolescence, as demonstrated in studies such as those conducted by Hüppi et al. (1998). Another study used DTI to investigate changes in cortical grey matter and found developmental disparities in the anisotropy of the frontal cortex in comparison to the rest of the cortical grey matter, suggesting a higher vulnerability of the frontal cortex compared to other brain regions (McKinstry et al., 2002).

Reiss et al. (2004) showed that both grey matter and white matter volumes were significantly reduced in 8-year-old preterm born children compared to term born controls. Moreover, they observed a significantly lower white matter volume in male preterm-born children, whereas this difference was not observed in female preterm-born children. These findings indicate that males may be particularly susceptible to disruptions in white matter development.

Multiple studies (Miranda et al., 2006; Bouyssi-Kobar et al., 2018; Tortora et al., 2017) show that at term-equivalent age (TEA), VPT born infants have higher brain perfusion compared to TB controls in most brain regions. Kehrer et al. (2003) showed a threefold increase in cerebral blood flow (CBF) in newborn infants from 32 to 42 weeks of postmenstrual age (Nosarti et al., 2006; Ment and Vohr, 2008). There are two main hypotheses for the higher CBF in prematurely born infants: (Bouyssi-Kobar et al., 2018) one such hypothesis suggests this difference may be due to an accelerated postnatal development at TEA, due to the extrauterine stimuli after birth. CBF values increase during the first months and years after birth in both VPT born children as well as in TB children (Kehrer et al., 2003; Wintermark et al., 2004; De Vis et al., 2012). This increase is explained by processes related to postnatal brain development including synaptogenesis, myelination, dendritic arborization, and functional activity processes (De Vis et al., 2012; Ouyang et al., 2017). Wintermark et al. showed that regions with high regional CBF coincided with regions of the brain that are under development (Wintermark et al., 2004), suggesting that the higher CBF observed in VPT neonates at TEA may arise from normal developmental changes postnatally due to longer postnatal time. The second hypothesis suggests that an impairment of autoregulation of cerebral blood flow in VPT infants is responsible for the increased CBF (Bouyssi-Kobar et al., 2018). Alterations in CBF during the neonatal phase have also been reported to play a role in the pathogenesis of peri- and neonatal brain injuries (Rhee et al., 2018). However, it is not known if these alterations in CBF persist into childhood and adolescence.

In healthy TB individuals, brain perfusion demonstrates marked developmental changes during childhood and adolescence, such that perfusion levels after birth first increase until approximately 5-6 years of age before declining markedly throughout childhood and adolescence, reaching adult levels by 15–19 years of age (Wintermark et al., 2004; Catherine et al., 1992). In contrast, the development of brain perfusion in VPT born children is not well understood to date. While one study reported lower perfusion within temporal regions, bilateral hippocampi and thalamus in adults born very low birth weight (<1500 g) (Pascoe et al., 2019), we found no study examining brain perfusion in VPT adolescents in relation to healthy controls. Alterations in brain perfusion during late childhood and adolescence may be related to the increased demands on academic functioning, which is closely linked to the maturation of executive functions. Further studies are therefore needed to determine if altered brain perfusion persists into childhood and adolescence for VPT individuals, and if alterations in perfusion are linked to difficulties in executive function.

Thus, the primary aim of the study was to explore possible differences in cerebral blood flow between VPT children and adolescents and term-born children and adolescents. A secondary aim was to investigate if perfusion is related to executive functions – the neurodevelopmental outcome most frequently impaired in this population.

2. Methods

2.1. Participant group

For this cross-sectional study, all examinations were performed between January and December 2013 at the University Children's Hospital in Zürich. The experimental design and the details of the participant cohort have been described previously (Wehrle et al., 2016, 2017, 2018) In summary, children and adolescents born very preterm were included in this study if they fulfilled the following criteria: 1. They were born < 32 weeks of gestation at the University Hospital in Zürich. 2. They had a non-pathologic neonatal ultrasound (with no signs of cystic PVL or hemorrhagic infarction). 3. They had no cerebral palsy or developmental delay at the routine checkup between the age of 4 and 8 years. 4. They were aged between 10 and 16 years at the time of the assessment. A group of age-matched term-born controls was recruited among friends and family of the participants or from local schools. Written informed consent was provided by a parent and by the participants older than 15 years, and oral consent was provided by the younger participants. The study was approved by the cantonal ethics committee of the canton of Zürich (KEK-ZH—Nr. 2012–0213).

Socioeconomic status (SES) was estimated using a six-point scale quantifying maternal education and paternal occupation (Largo et al., 1989), which was averaged between the two parents. In the case of children living in a single parent household, the SES from the single parent was used when this information was not available for both parents.

2.2. MRI data acquisition and analysis

Perfusion data were collected with a 3T GE MR750 MRI scanner using a background-suppressed, 3D pseudo continuous arterial spin labeling (ASL) sequence with a stack of spirals readout with repetition

time (TR) = 4600 ms, echo time (TE) = 10.5 ms, post-labelling delay = 1525 ms, field of view = 240 mm voxel resolution = 1.875 × 1.875 × 4 mm3). After a preliminary image quality-control assessment evaluating general image quality, noise and artifacts, 19 datasets were excluded because of bad image quality due to movement during imaging or the presence of braces (See Fig. 1). The images were normalized to a study specific perfusion template using FSL FLIRT (Jenkinson and Smith, 2001; Jenkinson et al., 2002).

High resolution 3D T1-weighted spoiled gradient echo images were also acquired with matrix = 256×256, 1 × 1 × 1 mm resolution, TR = 11 ms, TE = 5 ms, inversion time (TI) = 600 ms, flip angle = 8°, for segmentation and calculation of brain volumes. The 3D T1 images were segmented in FreeSurfer version 5.3 (Dale et al., 1999).

2.3. Executive function assessment

Executive function (EF) tests included tests for verbal fluency (Regensburger Wortflüssigkeits-Test (RWT) Aschenbrenner et al., 2001), cognitive flexibility (Intra-/extra-dimensional shift Task (IES), working memory (Spatial working memory Task, SWM) and planning (Stockings of Cambridge, SOC) (Sharma, 2013). A composite EF score was derived for each participant after Z-transforming the total score from each task, using the mean and standard deviation of the control group. The Z-scores were used to ensure equal scaling among the tasks for an overall composite score, which was derived by averaging the four Z-scores from the four EF tasks (Rhee et al., 2018; Schnider et al., 2020b). A detailed description of the different tests and their execution can be found in a previous publication of the same cohort (Wehrle et al., 2016).

2.4. Statistical analysis

Whole-brain perfusion (WBP) was extracted from the images using a grey matter mask from the automatic anatomical labeling (AAL) template (Tzourio-Mazoyer et al., 2002). After checking for normality of the WBP values with a Shapiro-Wilk test, groupwise differences in WBP were tested using a univariate ANCOVA, with WBP as the dependent variable, age as a covariate, and group (VPT vs TB) and sex as fixed factors.

Groupwise differences in perfusion and correlations between perfusion and EF scores were tested on a voxel-wise basis with FSL randomize, (Winkler et al., 2014) covarying for the WBP, and correcting for multiple comparisons with threshold free cluster enhancement. By overlapping the regions showing significant groupwise differences and the regions showing a significant correlation with EF scores across all children, we aimed to identify areas where differences in perfusion in preterm children may be related to neurodevelopmental differences in EF. All analyses of the WBP were conducted with SPSS (IBM Corp. Released 2020. IBM SPSS Statistics for Windows, Version 27.0. Armonk, NY: IBM Corp). The significance level was set at $p \leq 0.05$ (two-tailed).

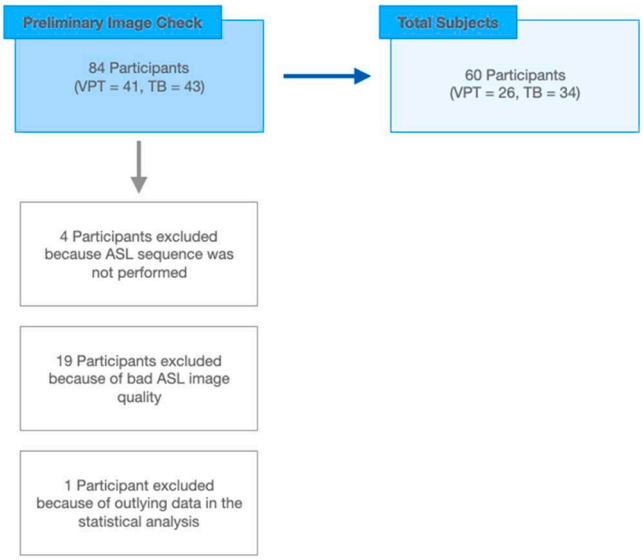

Fig. 1. Process of MR image selection.

3. Results

3.1. Sample characteristics

After exclusion (see Fig. 1), the final participant group consisted of 26 very preterm-born children and adolescents, born before 32 weeks of gestation (11 female, mean age 12.9, range 10.42–16.58 years) and 34 term-born control children (15 female, mean age 13.06, range 10.00–16.92 years). The excluded participants did not differ from the participants included in the ASL analysis in terms of age, sex, or IQ. In addition, the excluded VPT participants did not differ from the included VPT participants in terms of gestational age at birth, or birth weight (all $p > 0.3$).

The groups (VPT vs. TB) showed no significant difference in age, study timing (scan time during the day, since circadian effects have been reported to influence perfusion) (Hodkinson et al., 2014) and sex (15 [57.7 %] vs. 19 [55.9 %] Males, $p = 0.891$). However, there was a significant difference in the socioeconomic status (SES) of the two groups, with the preterm group demonstrating lower SES than the term-born controls. Nine of the children (7 VPT, 2 TB) were living in single parent households. The VPT group had a significantly lower EF summary score compared to the term-born group (see Table 1).

3.2. Perfusion and volumetric differences between children and adolescents born very preterm or at term

In the univariate ANCOVA, we found a significant effect of age with older adolescents, independent of group, having a lower WBP than the younger children. While there was no main effect of birth status, we found a significant interaction of birth status and sex on WBP ($p = 0.039$, Table 3), such that VPT girls showed lower perfusion than TB girls, but this trend was not seen in boys (see Fig. 2 and Table 2). Controlling for age and sex, there was no significant difference in total brain volume, cortical or subcortical grey matter volume, or white matter volume between VPT and TB groups (all $p > 0.117$). In addition, no significant group*sex interaction was seen for the brain volumes, although a significant age*sex interaction was seen for the cortical but not the subcortical grey matter volume.

The voxel-based analysis revealed regions in which brain perfusion was altered in VPT children compared to TB children, covarying for the WBP. As shown in Fig. 3, areas where VPT children showed higher relative perfusion than control children included the right thalamus, the right hippocampus, the right putamen as well as different regions of the right cerebral cortex and the cerebellum and brain stem. Regions where VPT showed significantly lower perfusion than control children included the putamen, the globus pallidus and the insula bilaterally as well as multiple regions of the cerebral cortex (Fig. 4).

3.3. Correlation between perfusion and executive functions

Across both groups, the EF summary score was significantly positively correlated to higher perfusion in the bilateral thalamus, right hippocampus, left caudate, bilateral putamen, bilateral amygdala, regions of the brainstem as well as various regions of the cerebral white matter (see Fig. 5). A subset of the regions showing a significant association between perfusion and the EF summary score, namely the right hippocampus and parahippocampal gyrus, right lingual gyrus, part of the right amygdala, right putamen as well as part of the brain stem

Table 1
Descriptive statistics of the very premature-born and term-born groups.

	VPT (n = 26)			TB (n = 34)			p
Male (n,%)	15 (57.7)			19 (55.9)			.891
	Mean	SD	range	Mean	SD	range	
Gestational age (weeks)	29.8	2.0	25.1 - 32.0			> 37	
Age at assessment (years)	12.9	1.7	10.4 - 16.6	13.1	2.1	10.0 - 16.9	.756
Socioeconomic status[a]	2.40	0.9	1.0 - 4.0	2.0	0.8	1.0 - 3.5	.045
Study Time (time of day)	14:01	03:44	8:09 - 18:43	13:37	03:31	9:06 - 19:19	.667
EF summary score	−0.55	0.77	- 2.00 - 0.61	−0.06	0.77	−1.94 - 1.15	.018

SD: standard deviation.
[a]1 = highest SES, 6 = lowest SES.

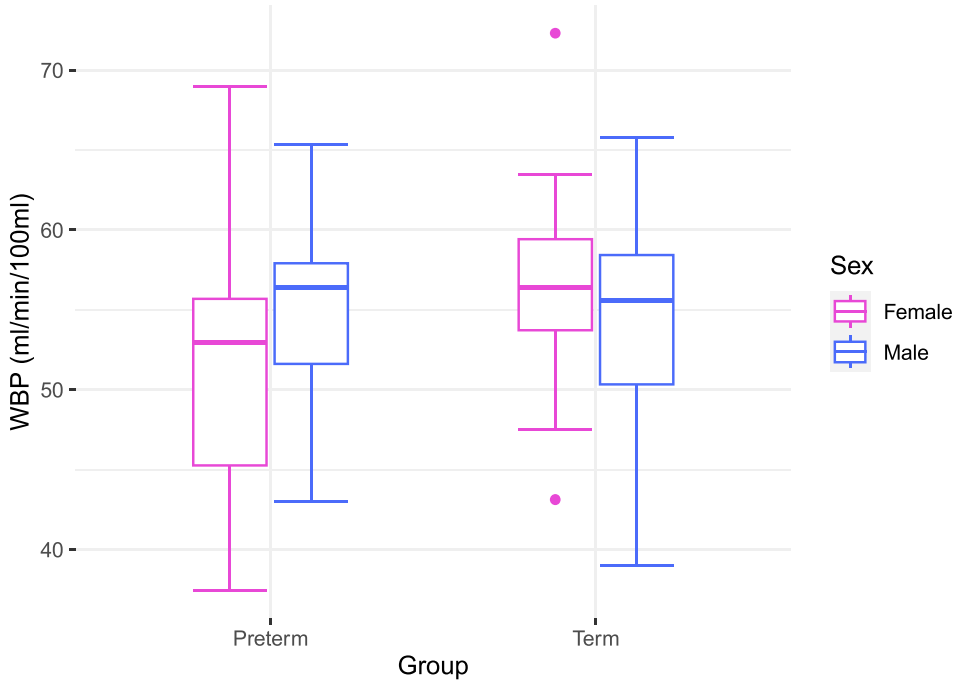

Fig. 2. Boxplot showing the birth status*sex interaction.

Table 2
Whole brain perfusion stratified by group and sex.

		WBP (ml/min/100 ml)			
		N	Mean WBP	SD	Range
VPT	Male	15	54.87	6.57	42.99 - 65.33
	Female	11	51.40	8.52	37.42 - 68.97
TB	Male	19	54.43	7.48	39.03 - 65.78
	Female	15	56.49	6.75	43.12 - 72.31

SD: Standard Deviation.

Table 3
Univariate ANCOVA with WBP as a dependent variable, covaried by age.

Source	SS	df	Mean Square	F	Sig.
Corrected Model	689.972	4	172.493	3.868	0.008
Intercept	6803.278	1	6803.278	11.712	< 0.001
Age	522.369	1	522.369	2.357	< 0.001
Birthstatus	105.129	1	105.129	0.02	0.130
sex	0.904	1	0.904	4.493	0.887
Birthstatus*sex	200.391	1	200.391		0.039
Error	2453.013	55	44.6		
Total	181,358.365	60			
Corrected Total	3142.984	59			

R Squared = 0.220 (Adjusted R Squared = 0.163).

(right-side), and the right thalamus overlapped with the regions showing significantly higher perfusion in VPT children (see Fig. 6 and Table 4). The association between perfusion and EF scores within this overlap cluster, in which the relative perfusion in VPT is significantly higher than in TB controls, and correlates significantly with EF, is shown in Fig. 7.

None of the regions showed a negative correlation between perfusion and the EF summary scores. None of the regions in which brain perfusion was higher in TB showed a correlation with EF scores.

4. Discussion

To our knowledge, the current study is the first to investigate differences in CBF between preterm-born and control adolescents and a possible link between perfusion and EF. The findings indicate that the average WBP is not different between VPT and TB born children and adolescents. However, we found an interaction regarding sex: The difference in WBP between VPT and TB was only found in girls but not in boys. Nevertheless, when examining perfusion on a voxel-wise level, controlling for the WBP, specific regions show locally increased or decreased cerebral brain perfusion (CBF) in VPT born children and adolescents. Visually, the areas of hypoperfusion in the VPT group relative to controls appeared to be more extensive than the areas of hyperperfusion in the VPT group, but a significant correlation between

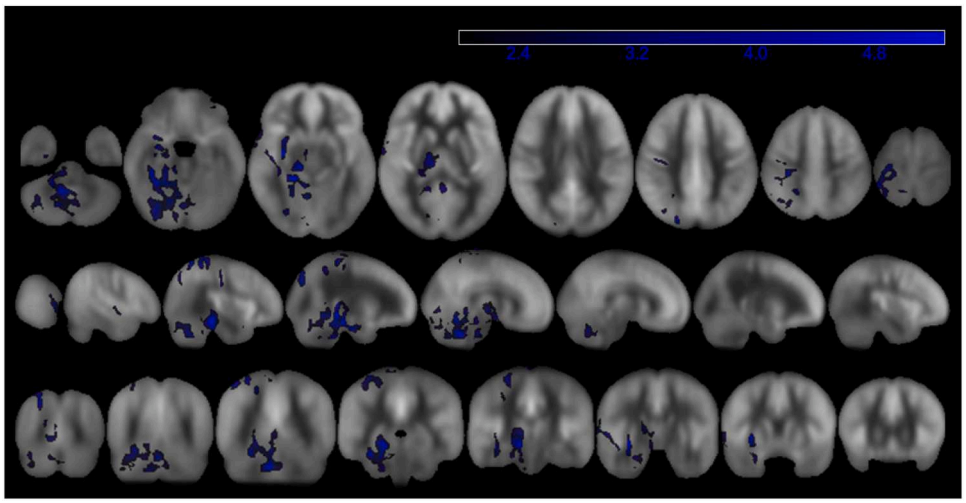

Fig. 3. Visual representation of the areas where brain perfusion is higher in VPT born children compared to TB controls. Statistical overlays are depicted as T-maps, thresholded at $p < 0.05$, corrected.

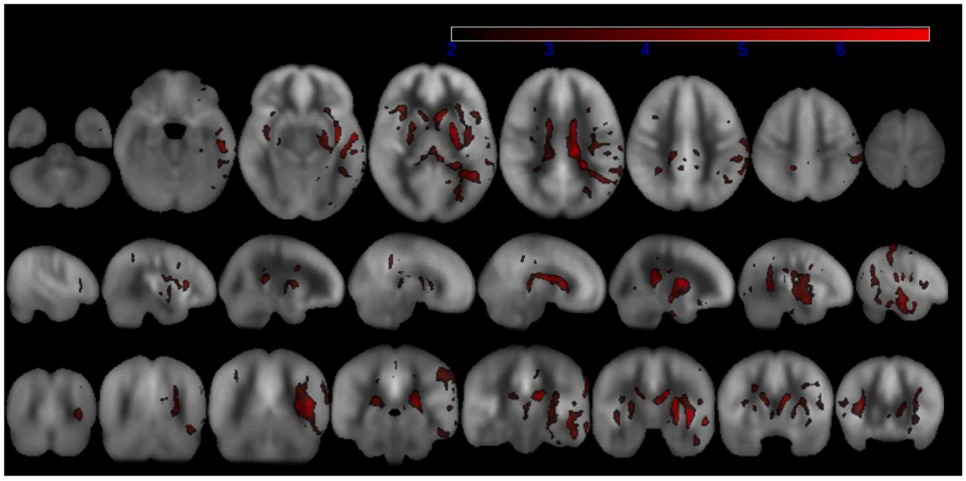

Fig. 4. Visual representation of the areas where brain perfusion is lower in VPT children compared to TB controls. Statistical overlays are depicted as T-maps, thresholded at $p < 0.05$, corrected.

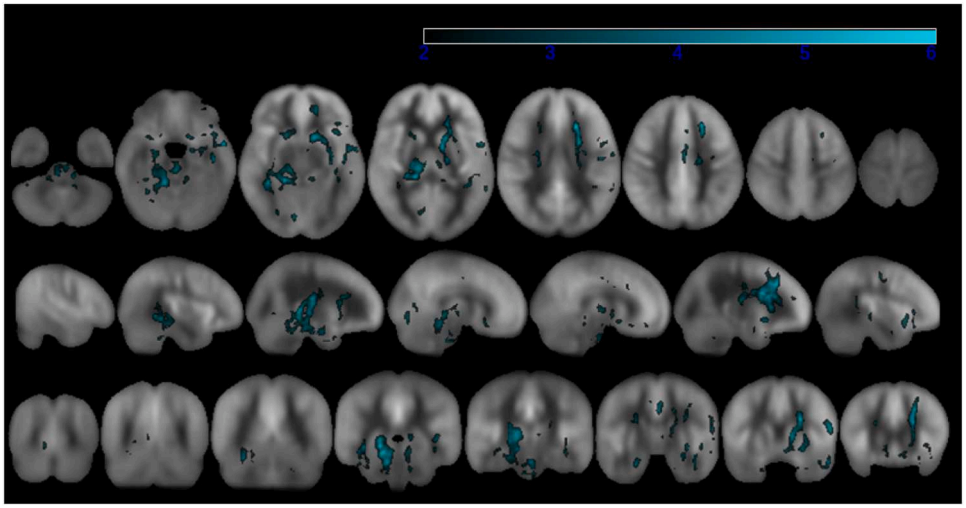

Fig. 5. Visual Representation of the areas where brain perfusion is positively correlated to the EF scores. Statistical overlays are depicted as T-maps, thresholded at $p < 0.05$, corrected.

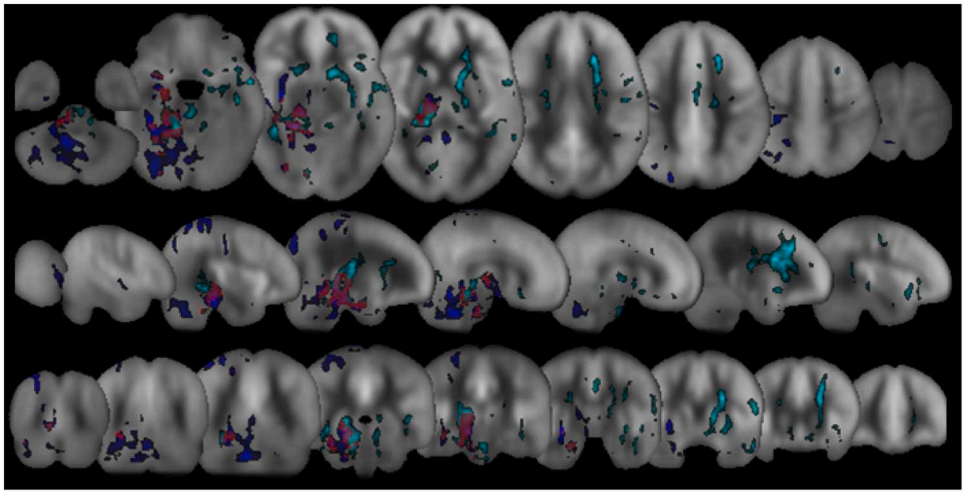

Fig. 6. Visual representation of the voxel-based analysis of brain perfusion differences between VPT and TB children. Areas in which perfusion in VPT > TB are shown in blue ($p < 0.05$, corrected). Areas in which perfusion is positively correlated to EF scores are shown in cyan ($p<0.05$, corrected). In red are the overlapping areas. Images are radiologically oriented (so the right brain is on the left and vice versa).

Table 4
List of peak coordinates and maximum T-statistics for sub-clusters demonstrating both a significant groupwise difference in perfusion and a significant correlation with executive function. (Sub-clusters were identified within the overlap cluster from Fig. 6, using the cluster command from fsl.).

Brain structure(s) (estimated from Harvard-Oxford Atlas)	Number of voxels	Max T-statistic MNI Coordinates			Max T-statistic VPT > TB	Max T-statistic EF correlation
		x	y	z		
Right parahippocampal gyrus Right lingual gyrus Right thalamus Right hippocampus Posterior cingulate gyrus Brain stem	4554	36	44	32	5.3	5.3
Right lingual gyrus Right occipital fusiform gyrus Right intracalcarine cortex	221	39	23	36	4.1	3.5
Right putamen	84	29	58	32	4.3	3.4
Right orbitofrontal cortex Right insular cortex	55	30	69	27	3.2	2.8

perfusion and EF was seen only in a subset of the areas showing hyperperfusion in VPT, as well as some brain regions with no significant groupwise differences in perfusion.

Our cohort included children and adolescents aged 10 to 16 years, meaning some of them were at the beginning of puberty or prepubertal, whilst older participants were possibly already at a later stage of puberty. This distinction is important since Satterthwaite et al. (2014) showed that during puberty there are multiple adaptations and changes in brain perfusion due to hormonal changes. In their research they showed that brain perfusion undergoes significant changes from the prepubertal age into puberty and found different developmental patterns of CBF evolution for boys and girls. Initially, CBF decreases for both boys and girls equally, but in girls brain perfusion tends to increase again starting at mid-puberty, whereas in boys it continues to decrease. Importantly, these developmental changes in perfusion are nonlinear and cannot be accounted for using a linear covariate for age, but covarying for the WBP, as was done in the voxel-wise analyses for the present study, should account for such age-, hormonal-, and sex-related changes exerting a global impact on perfusion. Accordingly, no interaction between group and sex was considered in the voxel-wise analyses.

Due to the relatively small group sizes, it was not possible to perform subgroup analyses in girls and boys separately, especially since the subgroups differed in their age distributions. Given the significant interaction effect and the main effect of age seen in our sample, in addition to the reports of differing developmental trajectories of perfusion reported in the literature for boys and girls, it would be interesting to examine the effects of very preterm birth on perfusion in a larger sample where subgroup analyses can be performed in girls and boys separately.

The developmental changes reported by Satterthwaite et al. (2014) may partly explain the higher perfusion seen in TB girls (in comparison to VPT girls) in our sample, since most TB girls were at the higher end of the age range. However, larger studies will be needed to confirm this finding, and further studies may also be able to clarify if the effects of very preterm birth on WBP remain consistent or show developmental changes during puberty.

Regarding the possible impact of preterm birth on the onset of puberty, a systematic review (James et al., 2018) including 16 studies yielded mixed findings. The majority of these studies either found no significant association between VPT birth and the timing of menarche in preterm-born girls or suggested an earlier onset of menarche in this group. In the case of males, most studies indicated no difference in the onset of puberty. The authors of the review concluded that the available evidence does not suggest that preterm birth significantly accelerates the onset of puberty. A more recent study by Suikkanen et al. (2022) confirmed these findings.

Regarding the regional perfusion, in the voxel-wise analysis, we observed that certain regions show significant differences in relative perfusion (covarying for WBP) between the VPT and the TB children. Regions in which TB children and adolescents show higher perfusion are located diffusely over both sides of the brain (slightly more left-sided). Interestingly, regions where VPT born children and adolescents have a significantly higher perfusion are predominantly on the right side of the brain and include some cortical regions, for example part of the superior parietal lobule, the lateral occipital cortex, postcentral gyrus, Heschl's Gyrus, and various subcortical regions including the right thalamus, the right hippocampus and the right putamen, as well as the cerebellum. These subcortical regions are known to be affected by preterm birth

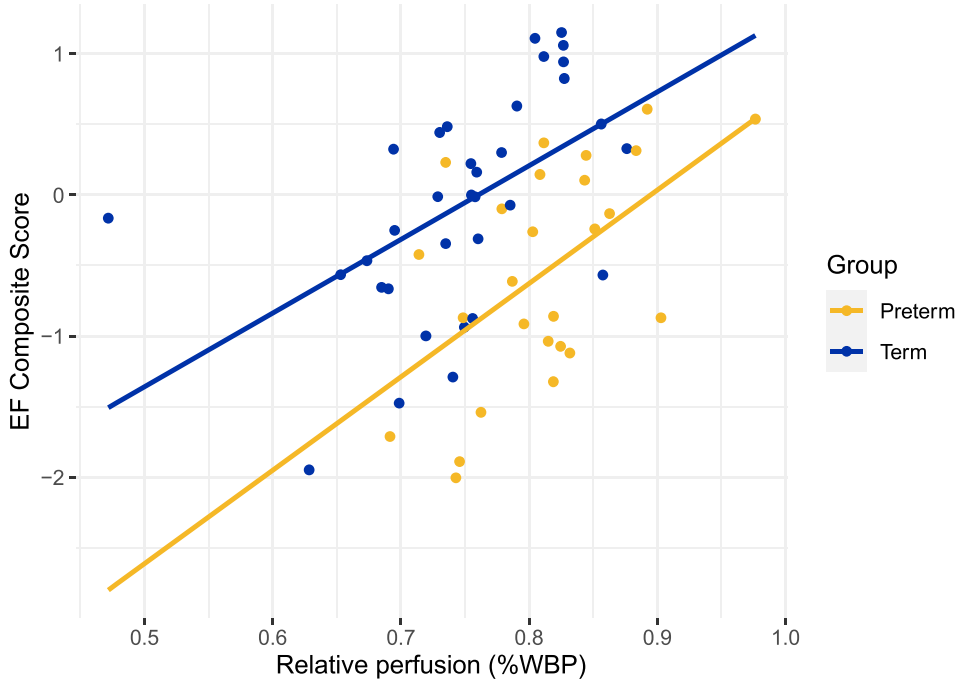

Fig. 7. Scatter plot showing the EF composite score vs relative perfusion in the overlap cluster, the region showing both a significant groupwise difference in perfusion and a significant association with EF scores, for each group.

(Volpe, 2009) The present cohort of VPT children and adolescents did not show injury to these regions on structural MRI, but the groupwise perfusion results indicate that these regions might show functional or physiological differences arising from preterm birth, even in the absence of structural changes. This indicates that residual effects may persist across childhood and adolescence.

The reason for the lateralization of our findings is unclear but may relate to developmental changes during the neonatal phase. Regional and hemispheric asymmetries of CBF have also been described in healthy term and preterm newborns by Lin and colleagues (Lin et al., 2013). They found that hemodynamic parameters like cerebral blood volume (CBV) and an index of cerebral blood flow (CBF_i) show regional differences with higher values in the parietal and temporal compared to frontal regions when measured in the neonatal period. Another interesting finding was the higher values of CBF_i in the right compared to the left hemisphere, with males presenting a more prominent right-left asymmetry. However, this study did not assess the extent of the asymmetry comparing preterm and term-born infants. Alterations in cerebral lateralization have also been described in VPT individuals for language regions and this abnormal lateralization appears to correlate with worse performance on language tests (Kwon et al., 2015). However, the basis for this lateralization in language function is not yet known (Kwon et al., 2015; Tseng et al., 2019; Scheinost et al., 2015; Gozzo et al., 2009). We did not compare structural correlates of the differences in brain perfusion, so further studies are needed to evaluate a link between our results on perfusion and the cerebral lateralization described by Kwon and colleagues. Alternatively, it is possible that the lateralization may just reflect a chance finding arising from a lack of statistical power, but larger studies are needed to confirm these findings.

Our results seem to partly disagree with the findings of Arditi et al. (2007). In their study they found a negative correlation between increased right cerebral blood flow velocity (CBFV) in the middle cerebral arteries and neurobehavioral maturation in premature and low birth weight children at 6, 12, and 24 months of age, meaning that a greater right CBFV absolute value was related to poorer performance on the habituation and orientation scales of the Neonatal Brazelton Behavior Assessment (NBAS) as well as a lower mental development index (MDI) of the Bayley Infant Development. Our study utilized a different neuroimaging method and focused on evaluating differences in CBF between VPT and TB and identifying possible correlations to the performance on EF assessments in childhood and adolescence. EF scores are known to be lower in VPT born children and adolescents, which we found to be true for our cohort. Additionally, our findings also show a higher relative perfusion in the right hemisphere of VPT born children and adolescents when compared to controls. The positive correlation of part of these right-sided areas with EF is not yet clear.

Earlier research has shown that VPT-born children score lower when tested for EF, [7,44] a result which was also replicated in the present study. In addition, we observed a significant positive correlation between EF and regional perfusion across both groups. Some of the regions in which perfusion is higher in the VPT group overlap with the regions where there is a significant positive correlation between perfusion and the composite EF score, such as the right hippocampus, part of the right amygdala as well as part of the brain stem (right-side), and the right thalamus. This could mean that VPT-born children and adolescents have higher baseline perfusion in these regions, possibly in compensation for functional deficits, although the lower EF score in preterm children indicates that any compensatory mechanism of perfusion, if present, does not fully compensate for EF deficits. However, none of the regions showing higher perfusion in term-born children correlated with the executive function scores. The clinical significance of the elevated perfusion in the TB group, or the reduced perfusion in the same regions in the preterm group, may therefore be limited but should be investigated further in a larger sample.

Executive functions have also been studied in fMRI studies of very preterm-born adults. In one study, load-dependent differences in functional activation have been reported during working memory tasks, and groupwise differences related to very preterm birth have also been observed for the more challenging level of a verbal fluency task (Hadaya and Nosarti, 2020) In addition, Nosarti et al. [19] have reported a complex pattern of (increased and decreased) hemodynamic responses to executive function tasks in preterm-born adolescents, in areas including the basal ganglia, thalamus, and para-hippocampal regions, as well as the insula and the cerebellum, that partly overlap with brain regions we

found to have altered CBF. However, these studies did not include a baseline perfusion assessment, so the potential influence of altered baseline perfusion on the altered hemodynamic responses observed during various EF tasks is not yet clear.

We did not find significant differences between VPT and TB children in the (pre)frontal cortex. Historically, executive functions were thought to be linked almost exclusively to frontal areas of the brain, leading to the term "frontal functions" being used as synonym for "executive functions" (Alvarez and Emory, 2006). Past neuroimaging and lesion studies have suggested that executive functions are associated with specific regions of the prefrontal cortex like the dorsolateral prefrontal cortex (DLPFC), the anterior cingulate cortex (ACC) and the orbitofrontal cortex (OFC) (Alvarez and Emory, 2006; Heyder et al., 2004). However, a meta-analytic review done by Alvarez and Emory (2006) has highlighted the finding that both frontal brain regions as well as non-frontal brain regions are necessary for executive functioning. These non-frontal regions include subcortical brain regions [59], brain stem sites and regions of the cerebellum (ventral tegmental area), and the substantia nigra (Koziol et al., 2012). In the current study, the thalamus, one of the subcortical regions known to be involved in executive functioning (Heyder et al., 2004), was found to have a higher CBF as well as a positive correlation to executive functions in VPT children and adolescents, possibly suggesting a compensatory mechanism due to altered brain development after very preterm birth.

4.1. Limitations

Because of the strict inclusion criteria (i.e., normal cranial ultrasound, and a normal developmental follow-up), our cohort of VPT-born children was rather high functioning. By excluding those with neonatal brain injuries we may have excluded those cases with more severe cognitive impairments, resulting in lower effect sizes relative to the control group. The high-functioning nature of the VPT group may also explain the lack of a significant difference in cortical or subcortical grey matter volumes, white matter volume, or total brain volume. However, since most of the VPT neonates grow to be quite healthy and high functioning (Purisch and Gyamfi-Bannerman, 2017) the VPT children and adolescents of our cohort represent the majority of the contemporary VPT population, making our results generalizable.

Since our cohort included only 26 VPT and 34 TB children, it was not possible to further subdivide into males/females and younger (beginning of puberty)/older (well into puberty) children. This complicated the interpretation of our results since puberty influences the trajectory of CBF development. In addition, while the analyses of the whole brain perfusion utilized a grey matter mask to try to reduce partial volume effects, systematic differences in normalization to the template between the VPT and TB groups could potentially introduce errors into the derived perfusion values. Such differences in normalization could arise from differences in brain volume or shape, and could impact the perfusion values derived on the whole brain and/or voxelwise level. In the present cohort, the lack of significant groupwise differences in volume or a significant group*sex interaction in brain volumes suggest that the observed interaction on perfusion is unlikely to be driven by volumetric differences. However, future studies should evaluate the perfusion with and without correction for regional grey matter volume, in order to confirm these findings and investigate the association between volumetric and perfusion changes associated with prematurity.

5. Conclusion

Our study shows that VPT adolescents without major neurological deficits show differences in perfusion within various brain regions in childhood and adolescence. In addition, perfusion decreased with age during adolescence and showed a significant interaction between birth status and sex, such that very preterm girls showed lower perfusion than term-born girls, but this trend was not seen in boys. When controlling for the WBP, the regions in which perfusion was regionally increased in VPT children are located mostly in the right hemisphere and some of these regions also show a positive correlation with executive functions. We found that the thalamus, a brain region well known to be involved in executive functioning, is one of the regions in which perfusion is higher in VPT and is positively correlated to executive function scores, suggesting that alteration in brain perfusion might partly be a compensatory mechanism in VPT individuals, but further studies are needed to confirm this. We also showed that there are regions in which brain perfusion is lower in VPT compared to TB children and adolescents. These regions are located mostly in the left hemisphere. However, these regions do not show any correlation to executive functions. Because of the influence puberty and sex have on CBF development during adolescence, further studies with bigger cohorts are necessary to evaluate CBF differences between VPT and TB children and adolescents independently of age and sex.

CRediT authorship contribution statement

Anna-Isabella S. Hijman: Formal analysis, Writing – original draft. **Flavia M. Wehrle:** Investigation, Project administration, Writing – review & editing. **Beatrice Latal:** Conceptualization, Writing – review & editing. **Cornelia F. Hagmann:** Conceptualization, Funding acquisition, Writing – review & editing. **Ruth L. O'Gorman:** Conceptualization, Methodology, Resources, Supervision, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data are available on request from the authors, subject to a formal data sharing agreement and approval from the local ethics committee.

Acknowledgments

This work was supported by the Zurich Center for Integrative Human Physiology (ZIHP), the Anna Mueller Grocholski Foundation and the "For Women in Science"-grant by L'Oréal Foundation, the Swiss Commission for UNESCO and the Swiss Academics for Arts and Sciences and the Swiss National Science Foundation (SNSF).

Reference

Aarnoudse-Moens, C.S.H., Weisglas-Kuperus, N., van Goudoever, J.B., Oosterlaan, J., 2009. Meta-analysis of neurobehavioral outcomes in very preterm and/or very low birth weight children. Pediatrics 124, 717–728. https://doi.org/10.1542/peds.2008-2816. Preprint at.

Alvarez, J.A., Emory, E., 2006. Executive function and the frontal lobes: a meta-analytic review. Neuropsychol. Rev. 16, 17–42. https://doi.org/10.1007/s11065-006-9002-x. Preprint at.

Arditi, H., Feldman, R., Hammerman, C. & Eidelman, A.I. Cerebral blood flow velocity asymmetry, neurobehavioral maturation, and the cognitive development of premature infants across the first two years. (2007).

Aschenbrenner, S., Tucha, O. & Lange, K.L. Regensburger Wortflüssigkeits-Test (Regensburger verbal fluency test). (Hogrefe - Verlag für Psychologie, 2001).

Ball, G., et al., 2013. The influence of preterm birth on the developing thalamocortical connectome. Cortex 49, 1711–1721.

Bhutta, A.T., Cleves, M.A., Casey, P.H., Cradock, M.M., Anand, K.J.S, 2002. Cognitive and behavioral outcomes of school-aged children who were born preterma meta-analysis. JAMA 288, 728–737.

Blencowe MRCPCH, H., et al., 2012. National, regional, and worldwide estimates of preterm birth rates in the year 2010 with time trends since 1990 for selected countries: a systematic analysis and implications. Lancet 379, 2162–2172.

Bouyssi-Kobar, M., et al., 2018. Altered cerebral perfusion in infants born preterm compared with infants born full term. J. Pediatr. 193, 54–61. .e2.

Catherine, Chiron, et al., 1992. Changes in regional cerebral blood flow during brain maturationin children and adolescents. J. Nucl. Med. 33, 696–703.
Counsell, S.J., Boardman, J.P., 2005. Differential brain growth in the infant born preterm: current knowledge and future developments from brain imaging. Semin. Fetal Neonatal Med. 10, 403–410. https://doi.org/10.1016/j.siny.2005.05.003. Preprint at.
Dale, A.M., Fischl, B. & Sereno, M.I. Cortical surface-based analysis I. Segmentation and surface reconstruction. http://www.idealibrary.com (1999).
De Vis, J.B., et al., 2012. Regional changes in brain perfusion during brain maturation measured non-invasively with arterial spin labeling MRI in neonates. Eur. J. Radiol. 82, 538–543.
Dibble, M., Ang, J.Z., Mariga, L., Molloy, E.J., Bokde, A.L.W., 2021. Diffusion tensor imaging in very preterm, moderate-late preterm and term-born neonates: a systematic review. J. Pediatr 232, 48–58.e3. https://doi.org/10.1016/j.jpeds.2021.01.008. Epub 2021 Jan 13.
European Perinatal Health Report. 2023 www.europeristat.com.
Gozzo, Y., et al., 2009. Alterations in neural connectivity in preterm children at school age. Neuroimage 48, 458–463.
Hüppi, P.S., et al., 1998. Microstructural development of human newborn cerebral white matter assessed in vivo by diffusion tensor magnetic resonance imaging. Pediatr. Res. 44, 584–590.
Hadaya, L., Nosarti, C., 2020. The neurobiological correlates of cognitive outcomes in adolescence and adulthood following very preterm birth. Semin. Fetal Neonatal Med. 25, 101117.
Heyder, K., Suchan, B., Daum, I., 2004. Cortico-subcortical contributions to executive control. Acta Psychol. (Amst) 115, 271–289.
Hodkinson, D.J., et al., 2014. Circadian and homeostatic modulation of functional connectivity and regional cerebral blood flow in humans under normal entrained conditions. J. Cereb. Blood Flow Metab. 34, 1493–1499.
James, E., Wood, C.L., Nair, H., Williams, T.C., 2018. Preterm birth and the timing of puberty: a systematic review. BMC Pediatr. 18.
Jenkinson, M., Smith, S., 2001. A global optimisation method for robust affine registration of brain images. Med. Image Anal. 5. www.elsevier.com/locate/media.
Jenkinson, M., Bannister, P., Brady, M., Smith, S., 2002. Improved optimization for the robust and accurate linear registration and motion correction of brain images. Neuroimage 17, 825–841.
Kehrer, M., Krägeloh-Mann, I., Goelz, R., Schöning, M., 2003. The development of cerebral perfusion in healthy preterm and term neonates. Neuropediatrics 34, 281–286.
Koziol, L.F., Budding, D.E., Chidekel, D., 2012. From movement to thought: executive function, embodied cognition, and the cerebellum. Cerebellum 11, 505–525.
Kwon, S.H., et al., 2015. Adaptive mechanisms of developing brain: cerebral lateralization in the prematurely-born. Neuroimage 108, 144–150.
Largo, R.H., et al., 1989. Significance of prenatal, perinatal and postnatal factors in the development of Aga preterm infants at five to seven years. Dev. Med. Child Neurol. 31, 440–456.
Lin, P.Y., et al., 2013. Regional and hemispheric asymmetries of cerebral hemodynamic and oxygen metabolism in newborns. Cereb. Cortex 23, 339–348.
McKinstry, R.C., et al., 2002. Radial organization of developing preterm human cerebral cortex revealed by non-invasive water diffusion anisotropy MRI. Cereb. Cortex 12, 1237–1243.
Ment, L.R., Vohr, B.R., 2008. Preterm birth and the developing brain. Lancet Neurol. 7, 378–379. https://doi.org/10.1016/S1474-4422(08)70073-5. Preprint at.
Miranda, M.J., Olofsson, K., Sidaros, K., 2006. Noninvasive measurements of regional cerebral perfusion in preterm and term neonates by magnetic resonance arterial spin labeling. Pediatr. Res. 60, 359–363.
Mulder, H., Pitchford, N.J., Hagger, M.S., Marlow, N., 2009. Development of executive function and attention in preterm children: a systematic review. Dev. Neuropsychol. 34, 393–421.
Nosarti, C., et al., 2006. Altered functional neuroanatomy of response inhibition in adolescent males who were born very preterm. Dev. Med. Child Neurol. 48, 265–271.
Nosarti, C., et al., 2014. Preterm birth and structural brain alterations in early adulthood. Neuroimage Clin. 6, 180–191.
Ouyang, M., et al., 2017. Heterogeneous increases of regional cerebral blood flow during preterm brain development: preliminary assessment with pseudo-continuous arterial spin labeled perfusion MRI. Neuroimage 147, 233–242.
Pascoe, M.J., Melzer, T.R., Horwood, L.J., Woodward, L.J., Darlow, B.A., 2019. Altered grey matter volume, perfusion and white matter integrity in very low birthweight adults. Neuroimage Clin. 22, 101780.
Peterson, B.S., et al., 2000. Regional brain volume abnormalities and long-term cognitive outcome in preterm infants. JAMA 284, 1939–1947.
Purisch, S.E., Gyamfi-Bannerman, C., 2017. Epidemiology of preterm birth. Semin. Perinatol. 41, 387–391. https://doi.org/10.1053/j.semperi.2017.07.009. Preprint at.
Reiss, A.L., et al., 2004. Sex differences in cerebral volumes of 8-year-olds born preterm. J. Pediatr. 145, 242–249.
Rhee, C.J., et al., 2018. Neonatal cerebrovascular autoregulation. Pediatr. Res. 84, 602–610. https://doi.org/10.1038/s41390-018-0141-6. Preprint at.
Satterthwaite, T.D., et al., 2014. Impact of puberty on the evolution of cerebral perfusion during adolescence. Proc. Natl. Acad. Sci. USA. 111, 8643–8648.
Scheinost, D., et al., 2015. Cerebral lateralization is protective in the very prematurely born. Cereb. Cortex 25, 1858–1866.
Schlapbach, L.J., et al., 2012. Outcome at two years of age in a Swiss national cohort of extremely preterm infants born between 2000 and 2008. BMC Pediatr. 12.
Schnider, B., et al., 2020a. Altered brain metabolism contributes to executive function deficits in school-aged children born very preterm. Pediatr. Res. 88, 739–748.
Schnider, B., et al., 2020b. Executive function deficits mediate the association between very preterm birth and behavioral problems at school-age. Early Hum. Dev. 146, 105076.
Sharma, A., 2013. Cambridge neuropsychological test automated battery. Encyclopedia of Autism Spectrum Disorders. Springer, New York, pp. 498–515. https://doi.org/10.1007/978-1-4419-1698-3_869.
Skranes, J., et al., 2012. Entorhinal cortical thinning affects perceptual and cognitive functions in adolescents born preterm with very low birth weight (VLBW). Early Hum. Dev. 88, 103–109.
Stålnacke, J., Lundequist, A., Böhm, B., Forssberg, H., Smedler, A.C., 2019. A longitudinal model of executive function development from birth through adolescence in children born very or extremely preterm. Child Neuropsychol. 25, 318–335.
Suikkanen, J., et al., 2022. Preterm birth and subsequent timing of pubertal growth, menarche, and voice break. Pediatr. Res. 92, 199–205.
Taylor, H.G., et al., 2011. Brain volumes in adolescents with very low birth weight: effects on brain structure and associations with neuropsychological outcomes. Dev. Neuropsychol. 36, 96–117.
Tortora, D., et al., 2017. Prematurity and brain perfusion: arterial spin labeling MRI. Neuroimage Clin. 15, 401–407.
Tseng, C.E.J., et al., 2019. Verbal fluency is affected by altered brain lateralization in adults who were born very preterm. eNeuro 6.
Tzourio-Mazoyer, N., et al., 2002. Automated anatomical labeling of activations in SPM using a macroscopic anatomical parcellation of the MNI MRI single-subject brain. Neuroimage 15, 273–289.
Vogel, J.P., et al., 2018. The global epidemiology of preterm birth. Best Pract. Res. 52, 3–12. https://doi.org/10.1016/j.bpobgyn.2018.04.003. *Clinical Obstetrics and Gynaecology*Preprint at.
Vollmer, B., et al., 2017. Correlation between white matter microstructure and executive functions suggests early developmental influence on long fibre tracts in preterm born adolescents. PLoS One 12, e0178893.
Volpe, J.J., 2009. Brain injury in premature infants: a complex amalgam of destructive and developmental disturbances. Lancet Neurol. 8, 110–124. https://doi.org/10.1016/S1474-4422(08)70294-1. Preprint at.
Wehrle, F.M., et al., 2016. Very preterm adolescents show impaired performance with increasing demands in executive function tasks. Early Hum. Dev. 92, 37–43.
Wehrle, F.M., Latal, B., O'Gorman, R.L., Hagmann, C.F., Huber, R., 2017. Sleep EEG maps the functional neuroanatomy of executive processes in adolescents born very preterm. Cortex 86, 11–21.
Wehrle, F.M., et al., 2018. Altered resting-state functional connectivity in children and adolescents born very preterm short title. Neuroimage Clin. 20, 1148–1156.
Wehrle, F.M., et al., 2020. Multimodal assessment shows misalignment of structural and functional thalamocortical connectivity in children and adolescents born very preterm. Neuroimage 215, 116779.
Winkler, A.M., Ridgway, G.R., Webster, M.A., Smith, S.M., Nichols, T.E., 2014. Permutation inference for the general linear model. Neuroimage 92, 381–397.
Wintermark, M., et al., 2004. Brain perfusion in children: evolution with age assessed by quantitative perfusion computed tomography. Pediatrics 113, 1642–1652.