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REVIEW ARTICLE

Brain tissue volumes in preterm infants: prematurity, perinatal risk factors and neurodevelopmental outcome: A systematic review

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***Objective*: To evaluate the clinical value of neonatal brain tissue segmentation in preterm infants according to the literature. *Methods*: A structured literature search was undertaken in MEDLINE/Pubmed. This included all publications on volumetric brain tissue assessment in preterm infants at term-equivalent age (TEA) compared to brain tissue volumes of term-born infants, related to perinatal risk factors or related to neurodevelopmental outcome. *Results*: Sixteen prospective cohort studies, described in 30 articles, fulfilled the criteria. Preterm infants displayed total and regional brain tissue alterations compared to healthy, term-born controls. These alterations seemed more prominent with decreasing gestational age. White matter injury, intraventricular haemorrhage, postnatal corticosteroid therapy, intra-uterine growth retardation and chronic lung disease were frequently associated with volume changes. Associations between volume alterations at TEA and neurodevelopmental outcome in early childhood were shown in a few studies. *Conclusions*: Preterm birth is associated with brain tissue volume alterations that become more pronounced in the presence of perinatal risk factors and white matter injury. Moreover, associations between volumetric alterations as early as TEA and long-term neurodevelopmental impairments are scarce.**

Keywords: preterm infant, volumetric measurements, brain segmentation, perinatal risk factors, neurodevelopmental outcome

Abbreviations: A, Automatic segmentation method; AGA, Appropriate weight for gestational age; BPD, Bronchopulmonary dysplasia; BS, Brainstem; BSID, Bayley Scales of Infant Development; BW, Birth weight; CA, Corrected age; CB, Cerebellum; CGM, Cortical grey matter; cHCV = mHCV –g(mICV-avgICV), Corrected hippocampal volume = measured hippocampal volume gradient of regression line between full-term hippocampal volume and ICV (measured ICV of full-term infants – average ICV of full-term infants); CLD, Chronic lung disease; CNS, Central nervous system; CPAR, Cerebral parenchyma; c-PVL, Cystic periventricular leukomalacia; CRIB, Clinical risk index for babies; CSF, Cerebrospinal fluid; cUS, Cranial ultrasound; FTF, Five to fifteen (questionnaire on development and behavior); GA, Gestational age; HC, Head circumference; HFV, High frequency ventilation; HINE, Hammersmith Infant Neurological Examination; ICV, Intracranial volume; IVH, Intraventricular haemorrhage; IUGR, Intra-uterine growth restriction; L, Left; M, Manual segmentation method; MDI, Mental development indices; MRI, Magnetic resonance imaging; MSML, Multisearch multilocation; MV, Mechanical ventilation; MWM, Myelinated white matter; NEPSY-II, Developmental Neuropsychological Assessment-II; N, Number; NDI, Neurodevelopmental impairment; including cerebral palsy, cognitive impairment defined as MDI < 70, hearing loss and blindness; NEC, Necrotizing enterocolitis; NR, Not reported; NS, Not significant; PDA, Patent ductus arteriosus; PDI, Psychomotor developmental index; PHVD, Post-hemorrhagic ventricular dilatation; PMA, Post menstrual age; PVL, Periventricular leukomalacia; R, Right; S, Semi-automatic segmentation method; SGM, Subcortical grey matter; TBT, Total brain tissue (cerebral and cerebellar parenchyma); TEA, Term-equivalent age; UK, Unknown; UWM, Unmyelinated white matter; VN, Ventricles; WM, White matter; WMI, White matter injury

Introduction

Despite improvements in survival rates and a decline of the incidence of cerebral palsy [1–5], a large number of very low birth weight children who survive without severe disabilities will still exhibit mild impairments in early childhood. Neurobehavioral impairments associated with brain immaturity occur even in the absence of significant brain lesions and have been related to more subtle alterations in brain development [6–8].

In the late 1990s, Hüppi and colleagues [9] were the first to document marked maturational changes in brain tissue volumes from 29 to 41 weeks post conceptional age, using a volumetric brain tissue segmentation technique. Results showed a fourfold increase in cortical gray matter (CGM) and a fivefold increase in myelinated white matter (MWM) in prematurely born infants. This emphasizes the vulnerability of the brain, due to rapid evolution of myelination and neuronal differentiation in this critical period of brain development in an extra-uterine environment.

Volumetric measurements performed in childhood and adolescence following preterm birth have demonstrated reductions in brain volumes associated with neurodevelopmental and behavioral problems [10].

The first two authors contributed equally to this work.

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It is of interest to perform quantitative measurements already during the neonatal period, both before and at term-equivalent age (TEA). These early studies will enable us to assess early brain growth, evaluate the impact of perinatal risk factors and may give access to an early predictor of long-term neurodevelopmental consequences.

Neonatal brain tissue segmentation is, however, considerably more difficult than tissue segmentation in adults or children. This is largely due to different tissue intensities compared to the adult brain and rapid development and growth of the infant brain. Several semi-automated and automated neonatal segmentation methods have been developed in recent years [11–14]. In this review, the focus will be on clinical applications of neonatal brain segmentation rather than on its methodology.

The purpose of the present review was threefold. The first aim was to provide a literature review with regard to volumetric assessment of preterm brain development. The second, to identify perinatal risk factors affecting brain volume. The third, to assess the additional value of neonatal brain volumetric segmentation in predicting long-term neurodevelopmental outcome in preterm infants.

Methods

A structured literature search was performed in MEDLINE/PubMed up to November 2011. Combinations and synonyms of the following keywords were used: 'preterm infant', 'term infant', 'MRI', 'segmentation', 'volume' and 'volumetric'. Articles were excluded if they did not involve original patient data, were published in another language than English or described technical methods for brain tissue segmentation, or if they did not focus on infants born prematurely. Studies were eligible for inclusion if neonatal brain tissue segmentation in preterm infants at TEA was performed to a) assess the influence of preterm birth on brain development by comparing brain tissue volumes of preterm infants to those of term controls, b) evaluate the impact of perinatal risk factors on brain growth or c) examine the relationship between brain tissue volumes and neurodevelopmental outcome. Titles and abstracts as well as full text articles were independently screened by two authors (K.J.K. and K.K.). Additionally, reference lists of selected articles were hand searched. In case of disagreement, consensus was reached by discussion with the other authors. The initial search retrieved 1553 articles. Thirty titles were selected, referring to 16 study cohorts. The full search strategy is available online (Supplementary Table SI and Figure SI).

Results

Prematurity and brain tissue volumes at TEA

Cerebral tissues classes

Ten different cohorts were studied to establish the influence of preterm birth on brain tissue volumes (Table I) [15–29]. In all cohorts preterm born infants were compared with healthy term controls. The latter were generally recruited from the postnatal wards in the study hospitals. Preterm infants at term demonstrated reduced brain tissue volumes primarily in CGM, subcortical gray matter (SGM), MWM and cerebellum (CB), with a reciprocal increase in cerebrospinal fluid (CSF) compared to healthy term controls. Tissue reductions seemed to be most prominent in the more immature infants [15–18,24,26]. In some studies multivariable regression analysis showed that gestational age (GA) remained independently associated with volumetric data, even when correcting for other confounding perinatal factors. This suggests an intrinsic adverse effect of prematurity on brain development [17–19,26]. However, others did not confirm these findings [20–23,25,27,28].

Regional volumes

Several authors studied regional volume alterations following preterm birth at TEA. Mewes and colleagues found decreased MWM in the brainstem, internal capsule and cerebellar peduncles when comparing preterm infants at TEA with term born infants [19]. Unmyelinated white matter (UWM) volume was decreased in central and orbitofrontal regions [19,26]. Thompson and colleagues found a decreased SGM volume in central and parieto-occipital regions, with the latter including part of the basal ganglia [26]. This was confirmed by Srinivasan and colleagues, who found a significant reduction in nucleus lentiformis and thalamus in preterm infants at term, with most pronounced reductions in infants with supratentorial lesions [25]. Mewes and colleagues did not find a significant difference in SGM volumes between preterm born infants and term controls [19]. Results for CGM are inconsistent, as both region-specific increases and decreases were reported [22,26]. Peterson et al. showed increased volumes in the anterior parts of the CGM [22], supporting the results from their prior study [10] in 8-years-old preterm children in which they showed significantly larger prefrontal CGM regions in children born prematurely compared to term controls. An increase in CSF was noted by all authors in almost all cerebral regions [19,20,22,26].

To summarize, preterm birth is associated with regional and overall brain tissue alterations. However, it has not yet been fully elucidated whether these effects are merely due to prematurity itself or to a combination of perinatal risk factors.

Perinatal risk factors

The impact of perinatal risk factors on brain tissue volumes in preterm infants at TEA has been the focus of many studies and is outlined in Table II [17,18,21,23–27,30–41]. The effect of white matter injury (WMI) was most extensively studied, followed by the effect of intraventricular hemorrhage (IVH), intrauterine growth restriction (IUGR), postnatal corticosteroid therapy, chronic lung disease (CLD) and neonatal surgery.

White matter injury

WMI was associated with volume reductions in CGM and MWM and an increase in CSF volume. WMI was defined either on a five item scale (WM shortening on T1-weighted imaging, qualitative reduction in WM volume, apparent cystic abnormality, lateral ventricular size and the combination of corpus callosum size and maturation of cerebral myelination) or as periventricular leukomalacia (PVL), including both cystic and diffuse PVL [17,33]. In one of these studies, CGM volume did include the CB [17]. Infants with WMI displayed CB volume reductions in two studies [23,34], although another study failed to show any significant correlation [38]. Similarly, two studies demonstrated a volumetric reduction within the nuclei of the deep grey matter in the presence of WMI [15,25], where another study did not find significant differences [33].

Intraventricular hemorrhages

A reduction of CB volume in the presence of IVH was reported in one study [38], while another did not find significant differences [23]. This may be explained by the larger percentage of infants

Table I. Effect of prematurity on brain tissue volumes at term-equivalent age.

Author	N Preterm infants	Subject characteristics	N Term Controls	MRI field strength (Tesla)	Segmentation method	Main volumetric abnormalities	Analysis adjusted for	Absolute volumes (ml± SD)	
								Preterm infants at TEA	Term controls
*[I] Boardman 2006 [15]	62	- GA 24–33 wks - No cystic PVL, IVH grade III/IV, congenital CNS infections, porencephalic cysts and postnatal steroids	12	1.5	a	- ↑ CSF posterior horns lateral ventricles - ↓ SGM; mostly thalami and lentiform nuclei	none	NR	NR
*[I] Boardman 2007 [16]	89	- GA < 33 wks - No congenital anomalies, focal parenchymal lesions or PHVD	20	1.5	a	- ↑ CSF in lateral and third ventricles - = TBT (ns)	PMA scan	NR	NR
*[II] Inder 2005 [17]	119	- GA ≤ 32 wks or BW < 1500 g	21	1.5	s	- ↓ CGM - ↓ MWM - ↑ CSF	ICV	178 ± 41 13.5 ± 5.8 45.6 ± 22.1	227 ± 26 20.8 ± 12 28.9 ± 16.8
*[III] Limperopoulos 2005 [34]	75	- GA < 37 wks - No brain malformations, metabolic disease, congenital anomalies or infections	20	1.5	m/s	- ↓ CB	weight and HC percentile, PMA at scan	26.0 ± 3.7	27.9 ± 2.6
*[IV] Mewes 2006 [19]	23	- GA 28–33 wks and AGA without severe perinatal complications - No brain lesions, chromosomal abnormalities, congenital anomalies or infections - No parental medical/psychiatric illness, substance abuse or long-term medication treatment	15	1.5	m/s	- ↑ CSF - ↑ frontal CSF - ↓ UWM central region - ↓ UWM right inferior central region - ↓ MWM - ↓ MWM central region - ↓ MWM occipital region	CPAR	76.4 ± 33.9 21.0 ± 10.5 36.1 ± 6.0 6.8 ± 1.1 7.3 ± 2.4 3.7 ± 1.2 3.1 ± 1.4	48.9 ± 29.9 9.0 ± 6.1 40.2 ± 5.6) 8.0 ± 1.1 9.8 ± 3.8 4.8 ± 1.9 4.4 ± 1.9
*[IV] Mewes 2007 [20]	24	- GA 28–33 wks and AGA without severe perinatal complications - No brain lesions, chromosomal abnormalities, congenital anomalies or infections - No parental illness, substance abuse or long-term medication treatment	20	1.5	s	- ↓ MWM - ↑ ICV superior frontal region	PMA	7.3 ± 1.9 55.4 ± 9.1	9.7 ± 2.7 41.1 ± 7.5
*[V] Murphy 2001 [21]	11	- GA 23–31 wks and BW < 1500 g - No WMI, IVH - Subgroup of infants without postnatal dexamethasone treatment	14	1.5	s	- ↓ MWM - ↑ CSF	UK/NR	15.2 ± 8.5 60.1 ± 21.4	27.6 ± 10.1 32.9 ± 13.5
Peterson 2003 [22]	10	- Medically stable AGA preterm infants - No congenital or chromosomal anomalies	14	1.5	m	- ↓ CGM parieto-occipital regions - ↑ CGM anterior regions - ↓ R WM parieto-occipital region - ↑ L WM parieto-occipital region - ↑ VN in midbody, occipital and temporal horns	HC, PMA scan	NR	NR
*[II] Shah 2006 [23]	83	- GA ≤ 32 wks and BW < 1500 g - No congenital anomalies	13	1.5	m/s	- = CB (ns)	ICV	22.0 ± 5.0 (ns)	23.5 ± 5.0 (ns)
Srinivasan 2006 [24]	89	- GA < 34 wks - No metabolic disease, congenital anomalies or infections, pre-existing lesions or cerebellar abnormalities - Subgroup of infants without supratentorial lesions	15	1.5	m	- = CB (ns)	HC scan, weight scan, cerebral volume	26.1 (median)	26.9 (median)

(Continued)

Table I. (*Continued*)

Author	N Preterm infants	Subject characteristics	N Term Controls	MRI field strength (Tesla)	Segmentation method	Main volumetric abnormalities	Analysis adjusted for	Absolute volumes (ml± SD)	
								Preterm infants at TEA	Term controls
Srinivasan 2007 [25]	40	- GA < 34 wks - No metabolic disease, congenital anomalies or infections	8	3.0	m	- ↓ thalamus - ↓ lentiform nuclei	none	13.6 (median) 3.07 (median)	16.3 (median) 5.6 (median)
*[VI] Thompson 2007 [26]	202	- GA < 30 wks and/or BW < 1250 g - No congenital anomalies	36	1.5	s	- ↓ CGM - ↓ SGM - ↑ CSF - ↓ CGM in orbitofrontal region - ↓ UWM in orbitofrontal region - ↓ MWM in inferior occipital region - ↓ SGM in subgenual region - ↓ SGM in midtemporal region - ↓ SGM in parieto-occipital region - ↑ CSF in dorsal prefrontal region - ↑ CSF in premotor region - ↑ CSF in sensorimotor region - ↑ CSF in parieto-occipital region	ICV	159 ± 41 13.6 ± 3.9 46.0 ± 26.0 1.4 ± 0.8 3.8 ± 2.4 1.2 ± 0.9 0.3 ± 0.3 0.5 ± 0.5 0.5 ± 0.4 5.5 ± 3.5 4.0 ± 2.6 2.8 ± 2.0 3.9 ± 3.3	173 ± 32 15.6 ± 2.5 26.3 ± 11 2.1 ± 1.5 5.4 ± 3.1 1.4 ± 0.9 0.4 ± 0.4 0.7 ± 0.5 0.7 ± 0.3 2.0 ± 1.3 2.1 ± 0.9 1.4 ± 0.6 1.7 ± 1.0
*[VI] Thompson 2008 [27]	184	- GA < 30 wks and/or BW < 1250 g - No congenital anomalies	32	1.5	m/s	- = hippocampi (ns) - ↓ CGM - ↓ SGM	cHCV = mHCV –g(mICV-aveICV)	2.27 ± 0.26 (ns) 163.1 ± 23.7 13.7 ± 3.5	2.36 ± 0.21 (ns) 175.4 ± 23.5 15.7 ± 2.3
*[VI] Thompson 2009 [28]	184	- GA < 30 wks and/or BW < 1250 g - No congenital anomalies	32	1.5	m/s	- ↓ asymmetry hippocampi	TBT within hemisphere	R 1.13 ± 0.16 L 1.12 ± 0.16	R 1.19 ± 0.12 L 1.16 ± 0.13
Zacharia 2005 [29]	13	- GA < 37 wks - Normal MRI/cUS and enteral feeding on first day of life	12	1.5	s	- = CGM, UWM, MWM, CSF (ns)	ICV	NR	NR

N = number of subjects included in the analysis; * = report on the same study population; NR = not reported; UK = unknown; ↑ = increase in; ↓ = reduction in; = = no significant changes in; a = automatic; s = semi-automatic; m = manual.
AGA = appropriate weight for gestational age; BW = birth weight; CNS = central nervous system; cUS = cranial ultrasound; GA = gestational age; HC = head circumference; IVH = intraventricular haemorrhage; MRI = magnetic resonance imaging; PHVD = post-hemorrhagic ventricular dilatation; PMA scan = postmenstrual age at time of scan; PVL = periventricular leucomalacia; WMI = white matter injury; CB = cerebellum; CPAR = cerebral parenchyma; CSF = cerebrospinal fluid; CGM = cortical gray matter; ICV = intracranial volume; MWM = myelinated white matter; SGM = subcortical gray matter; TBT = total brain tissue (cerebral and cerebellar parenchyma); UWM = unmyelinated white matter; VN = ventricles; L = left; R = right; cHCV = mHCV –g(mICV-aveICV) = corrected hippocampal volume = measured hippocampal volume – gradient of regression line between full-term hippocampal volume and intracranial volume (measured intracranial volume of full-term infants – average intracranial volume of full-term infants).

Table II. Effect of perinatal risk factors on brain tissue volumes in preterm infants.

Author	N Preterm infants	Subject characteristics	Perinatal Risk Factor	MRI field strength (Tesla)	Segmentation method	Main volumetric abnormalities	Analysis adjusted for	Absolute volumes (ml± SD)	
								Risk factor present	Risk factor absent
Benders 2009 [30]	38	- GA < 37 wks and hydrocortisone treatment for CLD - No IUGR or cerebral lesions more severe than IVH/PVL grade I - Preterm controls matched for GA, gender and respiratory status	hydrocortisone	1.5	s	- = CGM, UWM, MWM, SGM, CB, CSF (ns)	GA + PMA scan	ns	ns
*[I] Boardman 2006 [15]		- GA 24–33 wks - No cystic PVL, IVH grade III/IV, congenital CNS infections, porencephalic cysts and postnatal steroids	diffuse WMI IUGR CLD sepsis	1.5	a	- ↓ SGM - = SGM - = SGM - = SGM	none	NR	NR
*[I] Boardman 2007 [16]	89	- GA < 33 wks - No congenital anomalies, focal parenchymal lesions or PHVD	CLD diffuse WMI IUGR sepsis	1.5	a	- ↓ TBT - = TBT - = TBT - = TBT	PMA scan	NR	NR
*[VII] Ekblad 2010 [31]	232	- GA < 37 wks and BW ≤ 1500 g	maternal smoking	0.23 / 1.5	m	- ↓ frontal lobe - ↓ CB - = SGM, TBT, VN (ns)	GA, BW, gender, PDA, IVH, BPD/CLD, NEC, sepsis, MRI equipment, maternal alcohol consumption	117.9 ± 18.9 23.1 ± 5.3 ns	127.3 ± 24.7 24.5 ± 5.0 ns
*[VI] Filan 2011 [32]	175	- GA < 30 wks and BW < 1250 g - No congenital anomalies	surgery	1.5	s	- ↓ SGM - ↓ UWM	GA, BW Z-score, gender, duration of respiratory support	10.9 ± 3.2 192 ± 36	14.0 ± 3.6 216 ± 30
*[V] Inder 1999 [33]	20	- GA < 32 wks - Ventilatory support no longer than 14 days	diffuse and cystic WMI	1.5	s	- ↓ CGM - ↓ MWM - ↑ CSF	none	157.5 ± 41.5 14.5 ± 4.6 64.5 ± 15.2	211.7 ± 25.4 23.1 ± 6.9 52.0 ± 24.1
*[II] Inder 2005 [17]	119	- GA ≤ 32 wks and BW < 1500 g	diffuse and cystic WMI < 27 wks GA days of respiratory support	1.5	s	- ↓ CGM - ↓ MWM - ↑ CSF - ↓ SGM - ↓ SGM	ICV	152 ± 32 12.5 ± 4.9 61.1 ± 21 7.4 ± 3.7 NR	182 ± 41 16.7 ± 6.7 40.9 ± 18.7 12.3 ± 4.2 NR
*[III] Limperopoulos 2005 [18]	75	- GA < 37 wks - No brain malformations, metabolic disease, congenital anomalies or infections	brain lesions days of HFV PDA longer hospitalization	1.5	m/s	- ↓ CB - ↓ CB - ↓ CB - ↓ CB	weight and HC percentile, PMA scan UK	19.7 ± 3.5 20.1 21.5 NR	26.0 ± 3.7 24.0 24.5 NR
*[III] Limperopoulos 2005 [34]	74	- GA < 32 wks - No brain malformations, metabolic disease, congenital anomalies or infections and combined cerebral and cerebellar lesions	IVH grade IV diffuse WMI CB haemorrhage	1.5	m/s	- ↓ CB - ↓ Cerebrum - ↓ CB - ↓ Cerebrum - ↓ CB - ↓ Cerebrum	none	18.4 ± 3.0 289.3 ± 37.1 20.1 ± 3.8 306.3 ± 43.8 15.9 ± 3.1 322.8 ± 36.7	24.7 ± 3.8 361.0 ± 44.1 24.7 ± 3.8 361.0 ± 44.1 24.7 ± 3.8 361.0 ± 44.1

(Continued)

Table II. (*Continued*)

Author	N Preterm infants	Subject characteristics	Perinatal Risk Factor	MRI field strength (Tesla)	Segmentation method	Main volumetric abnormalities	Analysis adjusted for	Absolute volumes (ml± SD)	
								Risk factor present	Risk factor absent
*[VIII] Lodygensky 2008 [35]	26	- IUGR preterm infants secondary to placental insufficiency - AGA infants matched for GA - No brain lesions, congenital malformations or severe perinatal complications	IUGR	1.5	m/s	- ↓ hippocampi - ↓ CGM	none	1.94 ±.24 152.4 ± 21.6	2.14 ±.21 180.6 ± 32.0
*[V] Murphy 2001 [21]	18	- GA 23–31 wks and BW < 1500 g - No WMI or IVH	dexamethasone	1.5	s	- ↓ CGM	GA, CRIB score	130.3 ± 54.0	200.6 ± 35.1
Parikh 2007 [36]	41	- BW ≤ 1000 g - No congenital CNS anomalies	dexamethasone	1.5	m/s	- ↓ CB - ↓ SGM and internal capsule	PMA scan, BW, BPD	–19.7% (95% CI 4.7–34.6) –20.6 % (95% CI 8.9–32.3)	NA
*[VII] Reiman 2008 [37]	103	- GA < 32 wks or BW ≤ 1500 g	BW Z-score Caesarean section	0.23 / 1.5	m	- ↓ TBT - ↓ SGM - ↓ CB	none	NR	NR
*[II] Shah 2006 [23]	83	- GA ≤ 32 wks and BW < 1500 g - No congenital anomalies	grade 2–4 WMI IVH	1.5	m/s	- ↓ CB - = CB (ns)	ICV	21.6 ± 4.5 21.9 ± 5.1 (ns)	23.6 ± 5.0 23.8 ± 3.5 (ns)
Srinivasan 2006 [24]	113	- GA < 34 wks - No metabolic disease, congenital anomalies or infections, pre-existing lesions or obvious cerebellar abnormalities	supratentorial lesions IUGR	1.5	m	- ↓ CB - ↓ CB	HC scan, weight scan, cerebral volume	18.9 (median) (17.4–21.6)‡ NR	26.1 (median) (24.9-26.8)‡ NR
Srinivasan 2007 [25]	40	- GA < 34 wks - No metabolic disease, congenital anomalies or infections	supratentorial lesions days of MV BPD days until full enteral feeding NEC sepsis	3.0	m	- ↓ thalamus - ↓ lentiform nuclei - = SGM - = SGM - = SGM - = SGM - = SGM	BW, GA, PMA scan, weight scan, HC birth, HC scan	10.4 (median) 1.7 (median) NR	14.0 (median) 3.07 (median) NR
*[IX] Tam 2011 [38]	168	- GA < 33 wks - No congenital anomalies or infections, no chromosomal abnormalities	IVH grade I–II IVH grade III-IV WMI	1.5	s	- ↓ CB - ↓ CB - = CB (ns)	PMA scan, CB haemorrhage	–1.4 (–2.4 –0.2)‡ –5.4 (–7.3 –3.4)‡ NR	NA NA NR
*[IX] Tam 2011 [39]	172	- GA < 33 wks - No congenital anomalies or infections, no chromosomal abnormalities	antenatal betamethasone postnatal dexamethasone postnatal hydrocortisone	1.5	s	- = CB (ns) - ↓ CB - ↓ CB	PMA scan, IVH, CB haemorrhage, duration of intubation, hypotension requiring medical intervention, study site	–0.24 (–0.64 –1.11)‡ (ns) –2.33 (–3.52 –1.10)‡ –1.88 (–2.91 –0.86)‡	NA NA NA
*[VI] Thompson 2007 [26]	202	- GA < 30 wks and/or BW < 1250 g - No congenital anomalies	grade 3–4 WMI IUGR BPD postnatal steroids IVH	1.5	s	- ↓ dorsal prefrontal region - ↓ four posterior regions - ↓ occipital regions - ↓ overall volume	ICV	UK NR	NR NR

Table II. (*Continued*)

(*Continued*)

Author	N Preterm infants	Subject characteristics	Perinatal risk factor	MRI field strength (Tesla)	Segmentation method	Main volumetric abnormalities	Analysis adjusted for	Absolute volumes (ml± SD)	
								Risk factor present	Risk factor absent
*VI Thompson 2008 [27]	184	- GA < 30 wks and/or BW < 1250 g - No congenital anomalies	grade 3–4 WMI postnatal steroids indomethacin	1.5	m/s	- ↓ hippocampi - ↓ hippocampi - ↓ hippocampi	cHCV = mHCV – g(mICV-aveICV)	1.01 ± 0.12 1.03 ± 0.13 1.02 ± 0.11 1.02 ± 0.10 1.09 ± 0.13 1.11 ± 0.13	1.15 ± 0.13 1.16 ± 0.15 1.14 ± 0.13 1.16 ± 0.13 1.15 ± 0.13 1.17 ± 0.13
*[VII] Tolsa 2004 [40]	28	- IUGR preterm infants secondary to placental insufficiency - AGA infants matched for GA - No brain lesions, congenital malformations or severe perinatal complications	IUGR	1.5	s	- ↓ CGM	ICV	149.3 ± 29.2	189 ± 34.2
Vasileiadis 2004 [41]	23	- BW < 1500 - No IUGR, brain malformations, metabolic disease, congenital anomalies or infections, grade III/IV IVH, c-PVL or persistent ventriculomegaly	IVH grade I/II	3.0	s	- ↓ CGM	weight scan	102 ± 14.6	122 ± 12.9

N = number of subjects included in the analysis; * = report on the same study population; NA = not applicable; NR = not reported; ns = not significant; UK = unknown; ↑ = increase in; ↓ = reduction in; = = no significant changes in; a = automatic; s = semi-automatic; m = manual; ‡ = 95% confidence interval.

AGA = appropriate weight for gestational age; BPD = bronchopulmonary dysplasia (defined as persistent oxygen requirement at 36 weeks corrected age); BW = birth weight; CBH = cerebellar hemorrhage; CLD = chronic lung disease (defined as persistent oxygen requirement at 28 days of postnatal life); CNS = central nervous system; CRIB = clinical risk index for babies; GA = gestational age; HFV = high frequency ventilation; ICV = intracranial volume; IUGR = intra-uterine growth restriction; IVH = intraventricular hemorrhage; MV = mechanical ventilation; NEC = necrotizing enterocolitis; PDA = patent ductus arteriosus; PHVD = posthemorrhagic ventricular dilatation; PMA scan = postmenstrual age at scanning; PVL = periventricular leucomalacia; WMI = white matter injury; BS = brainstem; CB = cerebellum; CGM = cortical gray matter; CSF = cerebrospinal fluid; MWM = myelinated white matter; SGM = subcortical gray matter; TBT = total brain tissue (cerebral and cerebellar parenchyma); UWM = unmyelinated white matter; VN = ventricles; L = left; R = right; cHCV = mHCV –g(mICV-aveICV) = corrected hippocampal volume = measured hippocampal volume – gradient of regression line between full-term hippocampal volume and intracranial volume (measured intracranial volume of full-term infants – average intracranial volume of full-term infants).

with an IVH and/or the slightly higher percentage of severe IVH (grade 3 or 4 according to the Papile classification [42]) in the first study. A reduction in CGM associated with an IVH was found in one small cohort [41], whereas regional volumes including CGM did not differ in another cohort [26].

Intra-uterine growth retardation (IUGR)

IUGR was associated with significant volume reductions in CGM [40], hippocampus [35] and occipital regions (including brain stem and CB) [26], whereas there was a trend towards a lower CB volume [24]. Again in the study showing a reduction in CGM, CGM volumes did include the CB.

Postnatal corticosteroids

The effect of postnatal corticosteroid treatment was examined in five study cohorts and showed conflicting results [21,26,27,30,36,39]. Premature infants treated with dexamethasone exhibited significant decreases in CGM, CB, SGM and hippocampal volumes at term in four reports [21,27,36,39].

Thompson and colleagues found decreases in total brain volumes, although they could not demonstrate a significant effect of dexamethasone treatment on regional volumes after adjustment for CLD [26]. In the studies that showed significant relations between postnatal dexamethasone exposure and volume deficits, infants received relatively high cumulative doses of dexamethasone [21], or they were more immature and sicker than preterm infants who did not receive glucocorticoids during their stay on the neonatal intensive care unit [21]. Therefore, the impact of dexamethasone on subsequent brain growth needs to be elucidated in future studies, with adjustment for relevant clinical variables.

The impact of an alternative corticosteroid, hydrocortisone, on brain development was studied by Benders [30] and Tam [39]. Benders et al. did not find significant differences in cerebral tissue classes or CB between preterm infants treated with hydrocortisone for CLD and age-matched controls [30]. In contrast, Tam et al. demonstrated a significant correlation between hydrocortisone treatment and decreased CB volumes at TEA [39]. However, a large part of their hydrocortisone treated group was also treated with dexamethasone or had cerebellar lesions, which likely influenced their study results.

Chronic lung disease

Boardman et al. showed a reduction in overall brain volumes in infants requiring supplemental oxygen at 28 days [16]. Thompson and colleagues found a trend toward a lower overall brain volume in the presence of CLD, defined as the need for supplemental oxygen at 36 weeks GA. When correcting for other factors, CLD did not reach significance [26].

Neonatal surgery

There is limited data about the effects of neonatal anesthesia and surgery. One study suggests a decrease in SGM and UWM volume in infants undergoing surgery [32]. However, no corrections were made for the influence of type and timing of surgery. This observed relation therefore warrants replication before any conclusions can be drawn.

In summary, several perinatal risk factors affect brain development in preterm infants. The pattern of these alterations varies between different risk factors: CGM, hippocampus and CB seem to be most often affected.

Brain volume at TEA related to long-term neurodevelopmental outcome

In five cohorts, described in seven papers, brain tissue volumes at TEA were related to neurodevelopmental outcome in infancy and early childhood, using a wide range of outcome measures (Table III) [22,27,35,43–46].

Peterson and colleagues [22] were the first to examine relations between both total and regional brain tissue volumes and cognitive outcome. The authors reported significant associations between WM volumes in the right sensorimotor and right midtemporal regions and Mental Development Indices (MDI) on the Bayley Scale of Infant Development-II at 2 years corrected age (CA). These findings were confirmed in a larger study from another cohort, that revealed significant correlations between decreasing total cerebral tissue volumes in premotor, sensorimotor and parieto-occipital regions with subsequent increases in CSF and decreasing task performance on an object working memory task [46].

In the same large cohort, significant decreases in CGM and SGM were demonstrated with reciprocal increases in CSF in premature infants with moderate to severe disability at 12 months CA [17]. However, in this study CGM and UWM volumes included the CB. A third study in the same patient cohort could not find an association between – manually delineated – cerebellar volumes and neurodevelopmental outcome at 24 months CA [23].

Hippocampal volume

The relationship between hippocampal volumes at TEA and neurodevelopmental outcome was investigated in two different studies [27,35,43]. Lodygensky and coworkers showed marked reductions in the hippocampal volume associated with functional behavioral differences at TEA in all six subdomains of the Assessment of Preterm Infants' Behavior and associated with MDI at 24 months CA [35]. Beauchamp and colleagues [43] reported a comparable cohort of preterm infants. Associations between MDI and hippocampal volumes diminished after adjustment for social risk, thereby emphasizing the importance of caregiver education and social status for cognitive outcome. This stresses the importance of adequate adjustments for relevant demographic factors in statistical analyses.

Regional brain volumes

Lind and coworkers evaluated associations between regional brain tissue volumes at TEA measured on several MRIs with different field strenghts (0.23–1.5 T) and neurodevelopmental outcome at 2 and 5 years CA, respectively [44,45]. Preterm children with severe neurodevelopmental impairment at 2 years CA exhibited prominent reductions in tissue volumes of the cerebral parenchyma (CPAR), frontal lobes, SGM and CB with increases in ventricular volumes at TEA compared to preterm children without marked deficits [45]. These correlations partially persisted at the age of 5 years, as poorer scores on executive functioning and motor skills were associated with smaller tissue volumes of the CPAR and CB at term equivalent scan [44]. Yet, these results were based on a parental questionnaire and no significant associations between brain tissue volumes and the Developmental Neuropsychological Assessment-II domains could be demonstrated.

Thus, alterations in brain tissue volumes due to preterm birth appear to be associated with neurodevelopmental impairments in infancy and early childhood. These findings need to be interpreted with caution due to methodological differences and variability in statistical adjustments. Moreover, the additional clinical

Table III. Brain tissue volumes in preterm infants at term-equivalent age and neurodevelopmental outcome.

Author	*N* Preterm infants	Subject characteristics	Follow-up (months)	Outcome measure	MR field strength (Tesla)	Segmentation method	Main volumetric abnormalities	Analysis adjusted for	Absolute volumes (ml± SD)	
									Developmental delay	Normal development
*[VI] Beauchamp 2008 [43]	156	- GA < 30 wks or BW < 1250 g - No congenital anomalies	24	- MDI from BSID-II - working memory: delayed alternation task	1.5	s	- ↓ L hippocampus and ↓ working memory - ↓ R hippocampus and ↓ working memory - ↓ MWM and ↓ working memory	ICV, perinatal factors, MDI, social risk	R 1.10 ± 0.02 L 1.08 ± 0.02 9.4 ± 0.6	R 1.18 ± 0.03 L 1.16 ± 0.03 11.4 ± 0.6
*[II] Inder 2005 [17]	112	- GA ≤ 32 wks and BW < 1500 g - No congenital anomalies	12	- Denver Development Screening Tool	1.5	s	- ↓ CGM and moderate-severe disability - ↓ SGM and moderate-severe disability - ↑ CSF and moderate-severe disability	none	157 ± 41 8.4 ± 3.6 59.3 ± 28.8	181 ± 41 11.3 ± 4.2 44.3 ± 21.1
*[VII] Lind 2010 [44]	97	- GA < 37 wks and BW ≤ 1500 g - No congenital or chromosomal anomalies	60	- NEPSY II - FTF questionnaire	0.23	m	- ↓ TBT and ↓ executive functioning (FTF) - ↓ TBT and ↓ language (FTF) - ↓ CB and ↓ executive functioning (FTF) - ↓ CB and ↓ motor skills	BW, GA, IUGR, gender, parental level of education, brain lesions	NR	NR
*[VII] Lind 2011 [45]	164	- GA < 37 wks and BW ≤ 1500 g - No congenital or chromosomal anomalies	24	- MDI from BSID-II - HINE	0.23 / 1.5	m	- ↓ CB and NDI - ↓ frontal lobes and NDI - ↓ SGM and NDI - ↓ cerebrum and NDI - ↑ VN and NDI - ↓ CB and ↓ HINE in infants without NDI	none BW, GA, IUGR, gender, parental level of education, brain lesions	20 ± 6 111 ± 18 22 ± 3 327 ± 28 42 ± 61 NR	25 ± 5 130 ± 23 26 ± 5 369 ± 44 13 ± 8 NR
*[VIII] Lodygensky 2008 [35]	17	- IUGR preterm infants secondary to placental insufficiency - AGA infants matched for GA	24	- MDI from BSID-II	1.5	m/s	- ↓ hippocampi and ↓ MDI	none	NR	NR
Peterson 2003 [22]	10	- Medically stable AGA preterm infants - No congenital or chromosomal anomalies	18–20	- BSID	1.5	m	- ↓ WM R sensorimotor, R midtemporal regions and ↓ MDI	PMA scan, HC, GA	NR	NR
*II Shah 2006 [23]	83	- GA ≤ 32 wks and BW < 1500 g - No congenital anomalies	24	- BSID-II	1.5	m/s	- = CB and = MDI (ns) - = CB and = PDI (ns)	ICV, WMI	NR	NR

(Continued)

Table III. (*Continued*)

Author	*N* Preterm infants	Subject characteristics	Follow-up (months)	Outcome measure	MR field strength (Tesla)	Segmentation method	Main volumetric abnormalities	Analysis adjusted for	Absolute volumes (ml± SD) Developmental delay	Normal development
*[VI] Thompson 2008 [27]	UK	- GA < 30 wks and/ or BW < 1250 g - No congenital anomalies	24	- BSID-II	1.5	m/s	- ↓ L hippocampus and ↓ MDI	cHCV=mHCV–g(mICV-aveICV), gender, perinatal factors	NR	NR
*[II] Woodward 2005 [46]	92	- GA ≤ 32 wks and BW < 1500 g - No congenital anomalies	24	- BSID-II - working memory: MSML	1.5	s	- ↑ CSF and ↓ MSML - ↓ TBT and ↓ MSML - ↓ TBT premotor, sensorimotor and parieto-occipital regions and ↓ MSML	ICV total parcel	52.4 ± 28.3 402.4 ± 58.8 NR	38.0 ± 16.4 411.0 ± 31.8 NR

N = number of preterm infants included in the analysis; * = report on the same study population; NR = not reported; ↑ = increase in; ↓ = reduction in; = = no significant changes in; a = automatic; s = semi-automatic; m = manual.
AGA = appropriate weight for gestational age; BSID = Bayley Scales of Infant Development; BW = birth weight; FTF = Five to fifteen (questionnaire on development and behaviour); GA = gestational age; HC = head circumference; HINE = Hammersmith Infant Neurological Examination; IUGR = intrauterine growth restriction; MDI = Mental Developmental Index; MSML = multisearch multilocation; NDI = neurodevelopmental impairment including cerebral palsy, cognitive impairment defined as MDI <70, hearing loss and blindness; NEPSY-II = Developmental Neuropsychological Assessment-II; PDI = Psychomotor Developmental Index; PMA scan = postmenstrual age at scanning; WMI = white matter injury; CB = cerebellum; CGM = cortical gray matter; CSF = cerebrospinal fluid; ICV = intracranial volume; MWM = myelinated white matter; SGM = subcortical gray matter; TBT = total brain tissue (cerebral and cerebellar parenchyma); VN = ventricles; WM = white matter; L = left; R = right; cHCV = mHCV –g(mICV-aveICV) = corrected hippocampal volume = measured hippocampal volume – gradient of regression line between full-term hippocampal volume and intracranial volume (measured intracranial volume of full-term infants – average intracranial volume of full-term infants).

value of early MRI/MRI at TEA in predicting neurodevelopmental outcome in childhood has yet to be elucidated.

Discussion

Results of the present review suggest that preterm birth adversely affects brain development. Preterm infants show marked reductions in absolute volumes of MWM, CB and both CGM and SGM, accompanied by an increase in CSF volumes, in comparison to healthy term controls. This suggests delayed myelination and disruption of neuronal differentiation with atrophy due to preterm birth [15–17,19–21,25–27]. These alterations were observed even in the absence of severe perinatal complications [17–19,26] and appear to be more prominent in infants with the lowest GAs [15–18,24,26]. Regional vulnerability was primarily demonstrated for occipital and central regions [19,20,22,26]. WMI, IVH, IUGR, postnatal dexamethasone treatment and CLD were associated with brain tissue alterations in CGM, hippocampi, CB, CSF and both central and occipital regions, respectively, with WMI appearing to have the most pronounced adverse effect [16–18,21,33–36,40,41]. These disturbances seem to precede neurodevelopmental deficits. Total and regional volumetric alterations in predominantly CB, CSF and both central and parieto-occipital regions at TEA were related to neurodevelopmental impairment in early childhood [17,27,43–46].

Since WMI seems to have the most pronounced adverse effect on cerebral volumes, it is important to further elucidate the underlying pathophysiological mechanisms. MRI well before TEA is now becoming more easily accessible and increasingly utilized. Studies using serial MRI in the early neonatal period until TEA may help to clarify how white matter lesions evolve over time and how they affect brain maturation and/or structure thereby, providing additional information on early brain development that may no longer be visible at TEA. It may therefore be beneficial for the prediction of outcome to perform an MRI as soon as the infant is stable enough to be transported to the MR unit.

Data on neurodevelopmental outcome for preterm infants scanned at TEA is limited and long-term follow-up beyond 24 months CA is scarce [44]. Based on available evidence to date, tissue segmentation of neonatal brain MRI seems to be sensitive for predicting early neurodevelopmental delay as brain tissue reductions were detected in all infants manifesting neurodevelopmental deficits in early childhood. On the other hand, the majority of preterm born children who did show brain tissue alterations at TEA were found to show normal early development. Its specificity therefore appears to be low, which may partly be explained by the wide range and varying quality of the segmentation methods used. In order to adequately assess the potential of neonatal brain segmentation in predicting neurodevelopmental outcome in preterm infants, long term follow-up studies into late childhood are required, because the full extent of neurodevelopmental deficits does not become apparent until well into school age. Furthermore, it would be preferable to combine information obtained by several MR techniques, measuring cerebral volumes as well as connectivity or perfusion. This will improve the prediction of neurodevelopmental outcome, since it is unlikely that an explanation for an adverse neurodevelopmental outcome can only be explained by brain tissue volume deficits.

Several limitations should be taken into account when comparing the studies included in this review. Sample sizes showed great variability and inclusion criteria varied from medically stable and relatively healthy preterm infants in some studies to extremely low birth weight infants with concomitant brain injury in others. Considerable differences were also observed in

postmenstrual ages at time of the TEA scan. This heterogeneity in study cohorts hindered comparability of the results. Moreover, normalizing the data by correcting for intracranial volume and/or relevant perinatal variables was often not performed, which may have led to overestimation of observed effects. Furthermore, the influence of the level of education and social status of the primary caregiver on cognitive development in children is well known. Therefore both overestimation and underestimation cannot be ruled out without adequate adjustment for these relevant factors. The same holds true for gender differences, which were only taken into account in a few studies. Another limitation lies within the acquiring and post-processing of the imaging data. While most studies did use a 1.5 Tesla MR scanner, the PIPARI-study was partially undertaken on a 0.23 Tesla scanner [31,37,44,45]. Srinivasan [25] and Vasileiadis [41] were the only research groups who used a 3.0 Tesla system. Further, different automated and semi-automated image-processing algorithms were used to segment the MR-images into separate tissue classes, whilst some authors performed manual post acquisition volumetric measurements. Validation of the different algorithms showed important differences. For some algorithms, validation is unclear. Also, comparability of the different segmentation techniques is unknown. Studies using the method of Weisenfeld and Warfield [13] are of special concern, because CGM and UWM segmentations included CB tissue. This may have influenced the findings of reductions in CGM and UWM volumes in these studies, since these reductions may reflect a reduction in CB volume. This is important because there has been an increasing awareness of the strong correlation between cerebellar pathology and an adverse neurodevelopmental outcome [47] over the past couple of years.

Only a few studies have carried out parcellation of brain tissue for regional comparison of volumes and revealed region specific tissue reductions with reciprocal increases in CSF volumes. These studies focused on tissue differences between preterm infants and term controls, as well as on the impact of perinatal risk factors and the neurodevelopmental sequelae. These findings warrant replication, with a differentiation between the different tissue classes within the regions and a special interest to address the potential long-term effects of regional brain volume alterations on neurodevelopment.

Several limitations need to be addressed with regard to our systematic review as well. First, our search was limited to the MEDLINE/Pubmed database, only including articles published in English, which may have led to omission of relevant studies. Second, studies focusing on the effect of prematurity that did not involve healthy term controls were excluded, as well as studies reporting on other variables than clinical risk factors and those evaluating neurodevelopmental outcome without using cognitive or motor outcome measures for assessment of neurodevelopment. These criteria may have introduced a selection bias.

Despite these limitations, this is, to our knowledge, the first evaluation of the clinical applications of neonatal brain segmentation in preterm infants at TEA and the association with neurodevelopmental outcome.

Conclusion

Preterm birth often results in brain tissue alterations, which are related to the degree of immaturity at birth and the presence of perinatal risk factors, especially white matter injury. Changes in brain tissue volumes appear to be associated with neurodevelopmental deficits in early childhood. Future research is warranted to further elucidate the relationship between regional brain tissue alterations and long-term neurodevelopmental impairment. Validation of volumetric segmentation techniques should be carefully performed before implementation in clinical practice. One of the potentially most promising clinical implications of brain tissue segmentation is the identification of preterm infants eligible for neuroprotective interventions. It needs to be elucidated whether early preterm MRI provides additional information on brain maturation and early brain injury and, whether the combination of volumetric measurements with other imaging processing techniques (e.g. DTI, fMRI) can help to improve the prediction of neurodevelopmental impairment in this vulnerable group of infants.

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