Seminars in Fetal and Neonatal Medicine 24 (2019) 60–65

Contents lists available at ScienceDirect

Seminars in Fetal and Neonatal Medicine

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

Late preterm births: New insights from neonatal neuroimaging and neurobehaviour

Jeanie Ling Yoong Cheong[a,b,e,*], Deanne Kim Thompson[b,f,g,h], Joy Elizabeth Olsen[b,c], Alicia Jane Spittle[b,d]

[a] Newborn Research, Royal Women's Hospital, Parkville, VIC, Australia
[b] Victorian Infant Brain Studies, Clinical Sciences, Murdoch Children's Research Institute, Parkville, VIC, Australia
[c] Neonatal Allied Health Team, Royal Women's Hospital, Parkville, VIC, Australia
[d] Department of Physiotherapy, University of Melbourne, Grattan St, Parkville, VIC, Australia
[e] Department of Obstetrics and Gynaecology, University of Melbourne, Parkville, VIC, Australia
[f] Department of Paediatrics, University of Melbourne, Parkville, VIC, Australia
[g] Developmental Imaging, Murdoch Children's Research Institute, Melbourne, Australia
[h] Florey Institute of Neuroscience and Mental Health, Melbourne, Australia

ARTICLE INFO

Keywords:
Late preterm
Magnetic resonance imaging
Neurobehaviour
Premature
Infant

ABSTRACT

With increasing evidence of neurodevelopmental problems faced by late preterm children, there is a need to explore possible underlying brain structural changes. The use of brain magnetic resonance imaging has provided insights of smaller and less mature brains in infants born late preterm, associated with developmental delay at 2 years. Another useful tool in the newborn period is neurobehavioural assessment, which has also been shown to be suboptimal in late preterm infants compared with tern infants. Suboptimal neurobehaviour is also associated with poorer 2-year neurodevelopment in late preterm infants. More research into these tools will provide a better understanding of the underlying processes of developmental deficits of late preterm children. The value of their role in clinical care remains to be determined.

1. Introduction

Children born late preterm (LP), between 34 and 36 completed weeks' of gestation, are emerging as a group that deserve more attention than previously thought. Studies have reported more developmental delays in early infancy extending to school age [1–4]. In fact, the deficits described are not dissimilar to those described in the very preterm (< 32 weeks gestation) population, thus prompting the concept of a gestational age gradient [5] for developmental outcomes following preterm birth to extend to the LP period as well.

The human brain is rapidly developing during the later months of pregnancy. These processes are potentially disrupted by LP birth and its associated environmental or biological insults. For instance the growth trajectories of key brain regions such as the cerebral cortex, white matter, cerebellum, basal ganglia and thalami, and the hippocampus may be disrupted during this vulnerable period [6]. The functional organisation of the brain into integrated systems [7] or microstructural organisation may also be disrupted, including maturation of oligodendroglia to form myelin, and proliferation of white matter connections throughout the brain [8]. These processes can be probed using magnetic resonance imaging (MRI), a powerful non-invasive method for investigating the mechanisms of altered brain structure and function following LP birth.

Concurrent with the potential for disruption of normal brain development is the possibility that normal neonatal neurobehaviour is also affected by LP birth. This review summarises the current evidence around neuroimaging and neurobehaviour following LP birth. It is important to note that many studies combine both infants born in the LP period and moderate preterm (32–34 weeks gestation).

2. Neuroimaging

2.1. Modalities in newborns

The main modalities of neuroimaging in newborn infants are cranial ultrasound and brain magnetic resonance imaging (MRI). Cranial ultrasound has been used since the 1980s [9] and is still the mainstay neuroimaging investigation for preterm babies. It is portable and can be

* Corresponding author. Level 7, Newborn Research, Royal Women's Hospital, 20 Flemington Road, Parkville, VIC 3052, Australia.
E-mail address: jeanie.cheong@thewomens.org.au (J.L.Y. Cheong).

https://doi.org/10.1016/j.siny.2018.10.003

used for repeated scans even in unwell and unstable preterm infants. It is sensitive for detecting major brain injury such as intraventricular haemorrhage and cystic periventricular leukomalacia. These lesions, however, only make up around 9% of all preterm brain injury in extremely preterm infants (< 28 weeks gestation) [1,10]. Cranial ultrasound is less sensitive for the diffuse white matter lesions, which are more common compared with intraventricular haemorrhage or cystic periventricular leukomalacia.

Brain MRI is the most sensitive neuroimaging modality in preterm newborns. In addition to major brain injury detected on cranial ultrasound, brain MRI gives good information about brain maturation and size [11]. Using advanced MRI, brain volumes, microstructure, metabolism and functional parameters can be quantified. Thus, MRI is currently considered the reference standard for neuroimaging modalities in the newborn.

In clinical care, the LP infant does not usually warrant routine brain neuroimaging unless there are antenatal concerns, or significant postnatal events such as cardiovascular collapse or severe sepsis. Moreover, LP infants were previously thought to have very little morbidity compared with full term infants, and thus there was little interest in neuroimaging in this group of preterm infants. There is now a growing body of research suggesting that, akin to greater adverse neurodevelopmental outcomes, neuroimaging findings may also be abnormal in LP infants.

2.2. Cranial ultrasound

Several studies have reported cranial ultrasound findings in cohorts that include LP children. A single hospital study performed cranial ultrasound scans at 1 and 5 weeks in 1172 LP infants (34–36 weeks completed gestation) [12]. “Unfavourable” cranial ultrasound, defined as persistent periventricular hyperechogenicity, cysts, intraventricular haemorrhages, arterial strokes or venous malformations, were reported in 1.8% of cases at 5 weeks. Predictors of “unfavourable” scans included lower gestational age, Apgar score < 5 at 5 min and presence of comorbidities such as respiratory distress and hypoxic–ischaemic encephalopathy. Another single centre study of 724 infants born between 33 and 36 weeks reported cranial ultrasound abnormalities in 13% of the cohort, with the highest rates in those born most preterm (27.1% in 33 week infants compared with 3.7% in 36 week infants) [13]. The abnormalities included intraventricular haemorrhages, periventricular leukomalacia, cysts, or venous thrombosis. The study identified several perinatal associations with abnormal cranial ultrasound, including a head circumference measurement of < 3rd centile, ventilation or surfactant at birth, an Apgar score ≤6 at 5 min, and abnormal neurological examination in the neonatal period [13]. The higher rates in the second study likely reflect inclusion of more preterm babies compared with the first study.

A major limitation of these studies was the lack of correlation with neurodevelopmental outcome, which would have identified the clinical significance of such cranial ultrasound findings in LP infants.

2.3. Magnetic resonance imaging

2.3.1. Qualitative imaging and brain metrics

Magnetic resonance imaging (MRI) has revolutionised the understanding of brain development in very preterm newborns [14]. Many studies have demonstrated the presence of brain alterations as early as term-equivalent age in infants born < 32 weeks gestation compared with controls. Widely described findings are those of diffuse white matter injury, with decreased brain size of gray and white matter, deep nuclear gray matter and cerebellum in very preterm infants compared with term controls [14]. These MRI findings are associated with neurodevelopmental deficits, which have led to the concept of “encephalopathy of prematurity.” However, there is little research in the LP group compared with their more immature counterparts. Neuropathological studies suggest that the spectrum of brain injury described in the LP infant is similar to that found in very preterm infants [15]. This has been supported by findings from a recent MRI study of 199 moderate and late preterm (MLP) infants at term-equivalent age, and which compared neuroimaging findings with 50 term controls [16]. Using simple brain metric measurements, MLP infants had on average smaller brain measures (biparietal diameter, corpus callosum, deep nuclear gray matter and cerebellum), less mature brains (less myelination of the posterior limbs of the internal capsule and gyral folding) and larger extracerebral spaces, compared with controls. However, there was low prevalence of brain injury including white matter signal abnormalities, cysts or intraventricular haemorrhages compared with other studies in very preterm infants.

2.3.2. Quantitative imaging: brain volumes

As brain metric measures correlate with three-dimensional brain volumes [17], it would be expected that the alterations in three-dimensional brain volumes to be similar to that reported in qualitative MRI studies [16]. Brumbaugh et al. reported group differences of higher cerebrospinal fluid volumes and smaller total tissue volumes in LP 6–13-year-olds compared with full term controls [18]. The tissue volume differences were mostly driven by cortical and subcortical brain tissue, including the thalamus. In agreement with Brumbaugh et al., another study of LP children aged 6–12 years also reported smaller total brain volumes on average, and differences in gray matter volumes and cortical surface area in LP compared with term controls [19]. Interestingly, there are reports of differential findings in regional brain volumes between MLP infants at term equivalent age and controls. Alexander et al. [20] reported smaller brain volumes on average in some regions (such as cerebral white matter, middle temporal gyri, amygdalae, pallidum, and brainstem) but larger in other regions such as the primary visual, motor and somatosensory cortices with lower gestational ages. The differential finding of brain volumes in association with gestational age may reflect increased cortical development in response to increased sensory input and unrestricted motor output with greater time ex utero [21,22]. Another study reported the correlation between high density lipoprotein triglyceride levels with reduced gray matter volumes in LP infants at term-equivalent age compared with controls. This finding may suggest the possibility of high density lipoprotein triglyceride contributing to fatty acid transport and gray matter development during the postnatal period [23]. Clearly, more studies are needed in this area to replicate findings with larger cohorts.

2.3.3. Quantitative imaging: diffusion imaging

Diffusion MRI gives us a window into the microstructure of the brain. Although well studied in the very preterm infant, few studies have used this technique in the LP infant. Using a whole-brain approach (tract-based spatial statistics) in MLP infants at term-equivalent age compared with full term infants [24], Kelly et al. reported lower fractional anisotropy and higher mean, axial and radial diffusivities in moderate and LP infants compared with controls in the majority of the brain's major white matter fiber tracts. These widespread brain white matter microstructural alterations were consistent with delayed or disrupted white matter microstructural development [24]. Altered brain structural connectivity in LP compared with term-born individuals have also been reported in adolescence [25,26], which suggests that some of these differences persist long term.

Some studies have explored the complexity of brain network organisation using diffusion imaging, concluding that longer gestation was associated with more mature organisation of the brain in terms of communication within brain networks [27,28]. These studies would suggest that LP birth is associated with a less mature and organised brain compared with children born full term.

2.3.4. Quantitative imaging: resting state functional MRI

Resting state functional MRI (fMRI) is used to evaluate regional

interactions of the brain that occur in a "resting" state, i.e. when the participant is not particularly engaged in any task. Studies comparing resting state fMRI between moderate and LP newborns and term controls have reported altered neural activity in certain regions of the brain, such as the primary sensory and motor cortices, and primary somatosensory cortex [29]. Functional connectivity is also altered in adolescence, for those born moderate and LP compared with term controls [25,26].

2.3.5. Association with perinatal factors

Early life predictors (birthweight *z*-score, multiple birth, sex, postnatal growth and social risk) of brain volumes and brain microstructure in preterm children have been reported but there is little published specifically in the LP infant. Lower birthweight *z*-score and male sex are associated with diffusion measures that reflect a "less mature" brain, in many regions including the optic radiation, corpus callosum, and corona radiata [24]. There needs to be more work done in this area to identify risk factors associated with smaller brain volumes and "less mature" brain microstructural development in LP children.

2.3.6. Association with neurodevelopment

Although important to determine structural differences in the brain of LP children compared with term controls, the significance of these differences lies in any structure–function relationships. In a cohort of MLP infants, larger total brain tissue and white matter volumes were associated with higher cognitive and language scores at 2 years corrected age; and larger cerebellar volumes were associated with better language and motor scores, even after adjustment for other perinatal factors [30]. There may also be regional brain vulnerability that is associated with poorer function. Rogers et al. reported greater anxiety symptoms in 6–12-year-old LP children, which was mediated by the relative decrease in right temporal lobe volume [19].

Even less has been documented on the significance of the diffusion MRI findings in LP children in association with long-term neurodevelopment. It will be important to follow LP children into childhood and beyond, to track long-term brain development following LP birth, and how this relates to functional neurodevelopment.

2.3.7. Recommendations for neuroimaging for LP infants

There is currently insufficient evidence to recommend cranial ultrasound or brain MRI as a screening tool for LP infants. Given the large population of LP infants, and resource limitations, the current role of neuroimaging is mainly within the research context of understanding the underlying mechanisms and brain–behaviour relationships associated with LP birth.

3. Neurobehaviour

3.1. Neurobehavioural assessments in newborns

An infant's neurobehaviour encompasses their neurological status, such as muscle tone, reflexes, quality of movement and motor responses to stimuli, as well as their behavioural responses, including their ability to regulate and organise their state, and attentional, interactional capabilities [31]. How an infant responds during a neurobehavioural assessment provides insight into the integrity of their central nervous system, as well as their individual behavioural vulnerabilities and strengths [31,32]. Clinicians use neurobehavioural assessments to identify infants who may require additional developmental assessment and intervention, and to help parents understand and sensitively respond to their infant's individual behaviour to guide their development [32]. Much of the literature on neurobehavioural assessments has focused on infants born very preterm (< 32 weeks gestation) [33,34]. However, recent studies indicate that infants born MLP have alterations in their neurobehaviour as early as term-equivalent age, compared with term-born peers, and, importantly, these alterations are related to later developmental outcome, as well as neuroimaging findings [35,36]. Higher rates of brain abnormality are associated with higher rates of poorer neurobehaviour in MLP infants, and there is a clear continuum of neurobehavioural development with better neurobehavioural performance inversely related to decreasing gestational age, including within the MLP age group [35,36].

There are several neurobehavioural assessments available; the purpose of the assessment informs the clinician's choice of tools, and a combination of assessments provides a more comprehensive picture of the infant's abilities than a single assessment tool in isolation [32,37]. We outline three neurobehavioural assessments with robust psychometrics and clinical utility for MLP infants that provide complementary assessment of infant's neurobehaviour: the Hammersmith Neonatal Neurological Examination (HNNE) [38], the Neonatal Intensive Care Unit Network Neurobehavioral Scale (NNNS) [39], and Prechtl's qualitative General Movements Assessment (GMA) [40].

3.2. Hammersmith Neonatal Neurological Examination

The HNNE focuses on the infant's neurological status as well as some behavioural responses. It includes 34 items across six subscales: tone, tone patterns, reflexes, spontaneous movements, abnormal neurological signs and behaviour; these are added for a total score. An overall optimality score is calculated from the total score with suboptimal performance defined as scores < 10th centile according to healthy term infant norms [38,41], and reference values are available for infants born < 35 weeks gestational age at term-equivalent age [42]. At term-equivalent age in a cohort of 197 MLP infants, 25% had suboptimal total scores on the HNNE, as well as more variability in neurobehaviour compared with healthy term infants [41]. When followed up at 2 years corrected age, those infants with suboptimal HNNE spontaneous movements (odds ratio (OR): 3.13; 95% confidence interval (CI): 1.29–7.6; $P = 0.012$), abnormal signs (OR: 2.58; 95% CI: 1.19–5.61; $P = 0.016$), and total scores (OR: 2.98; 95% CI: 1.42–6.27; $P = 0.004$) had increased odds of cognitive delay on the Bayley III [36].

Suboptimal performance on the HNNE increases with decreasing gestational age, even within the LP age group [43]. In a study of 375 LP infants (born between 34 and 36 weeks gestation) assessed at term-equivalent age using the HNNE, infants born at 34 weeks had a different profile of scores than those born at 35 and 36 weeks gestation, and presented with lower flexor limb tone, poorer head control and visual orientation, than the infants born at the later weeks gestation [44]. This may be related to rapid brain growth and organisation occurring within this period; higher abnormality scores (global, white matter and cerebellar abnormality) are associated with lower HNNE scores on concurrent brain MRI [35]. When assessed in the first three days after birth, LP infants also have a wider range and variability in scores on the HNNE compared with term infants with lower trunk and leg flexor tone, and more abrupt movements, tremors, and startles [43].

3.3. Neonatal Intensive Care Unit Network Neurobehavioral Scale

The NNNS [39] assesses neurological function as well as the infant's behavioural organisation, and stress responses during the assessment. There are 45 administered items and the infant's behavioural responses are observed, comprising a total of 115 items. Thirteen summary scales are calculated according to term infant norms, with higher scores on the habituation, attention, regulation, and quality of movement scales indicating better neurobehaviour, and higher scores on the handling, arousal, excitability, lethargy, non-optimal reflexes, asymmetrical reflexes, stress, hypertonia, and hypotonia scales indicating worse neurobehaviour. Whereas the NNNS was originally developed for assessing drug-exposed infants [39], with specific poor neurobehavioural profiles on the NNNS at a corrected age of one month (poor regulation, tone abnormalities, high levels of stress and lethargy) being associated with adverse learning and behavioural outcomes at 4.5 years for infants

exposed to maternal substance use [45], there is evidence that the NNNS can also assist clinicians and researchers in understanding MLP neurobehaviour for infants that are not drug-exposed.

Prior to term-equivalent age, MLP infants have less mature neurobehaviour on the NNNS than term infants; in a study of neurobehaviour in the first two weeks after birth, MLP infants ($n = 209$) had worse mean and median scores for attention, quality of movement, hypotonicity, excitability, non-optimal reflexes, lethargy and stress compared with full-term infants ($n = 201$) [41]. In a smaller study ($n = 36$), LP infants (16) had poorer attention ($P = 0.04$), arousal ($P = 0.01$), regulation ($P \leq 0.001$), and quality of movement ($P \leq 0.001$), and higher rates of non-optimal reflexes ($P \leq 0.001$), and hypotonicity ($P = 0.03$) compared with term infants assessed in the first 24–72 h after birth; however, infants were not followed up at later ages.

When assessed at term-equivalent age, alterations in MLP infant neurobehaviour are still evident. In a study of term-equivalent neurobehaviour of infants born across gestational age groups (very preterm, $n = 149$; MLP, $n = 200$; full-term $n = 200$) MLP infants had double or greater rates of suboptimal neurobehaviour on NNNS for five subscales (regulation, arousal, quality of movement, excitability, and stress) compared with full-term infants [35]. Of note, at term-equivalent, MLP infants had similar rates of suboptimal attention, regulation, arousal, handling, quality of movement, and excitability on the NNNS as infants born very preterm, who are higher risk developmentally. Whereas very preterm infants had higher rates of non-optimal reflexes, hypertonicity, and hypotonicity than MLP infants, early indicators of behaviour (such as attention and stress) were considerably worse in the MLP than the full term group, and may provide early markers for later behavioural, cognitive and language difficulties seen in the MLP population [1].

In follow-up studies of MLP infants, suboptimal excitability (OR: 3.42; 95% CI: 1.67–7.02; $P = 0.001$), regulation (5.15; 2.47–10.75; $P < 0.0001$), and arousal (2.14; 1.04–4.40; $P = 0.038$) at term-equivalent were associated with increased odds of cognitive delay, and suboptimal lethargy scores were associated with increased odds of language (5.64; 1.33–23.85; $P = 0.019$) and motor delay (6.86; 1.64–28.71; $P = 0.008$) at two years corrected age on the Bayley III [36].

3.4. General Movements Assessment

Observation of the LP infant's quality of movement is an important component of the neurobehavioural assessment, and Prechtl's GMA [40] has high predictive validity for neurodevelopmental impairment. The GMA involves observation of specific spontaneous movements, termed general movements (GMs); these are whole body movements that are assessed according to age-specific characteristics, from prior to term, up until corrected age of 4 months. Normal GMs involve complex, fluent and variable movement patterns, whereas abnormal GMs tend to be monotonous in speed and amplitude, showing less fluency and lacking movement complexity [40]. Abnormal GMs are an early marker for cerebral palsy [46] and other neurodevelopmental impairments in preterm infants [47], and are associated with brain injury, white matter abnormality and poor brain growth [48,49]. There is a continuum of poorer quality of movement on the GMA with higher rates of abnormal GMA occurring with lower gestational ages [35,50]. In the first two weeks after birth, 75% MLP infants ($n = 80$) and 68% of LP infants ($n = 129$) had abnormal GMA, compared with 10% of full term infants ($n = 201$) [41]. In a study including 103 preterm infants (born < 36 weeks gestational age), and 12 term infants with brain injury, GMA had sensitivity of 100% and specificity of 84% for predicting neurodevelopmental outcome at 18 months corrected age [51]. Smaller studies using the GMA have included infants born MLP, predicting IQ at 7–11 years with sensitivity of 67% and specificity of 71% at 7–11 years [52], and high sensitivity (100%) but lower specificity (21%) for predicting motor impairment at 5–6 years [53] (Table 1).

Table 1
Relationships between neurobehavioural assessments and neurodevelopment.

Neurobehavioural assessment	Cognitive delay	Language delay	Motor delay
Hammersmith Neonatal Neurological	✓		
Examination [36] Poor	✓		
spontaneous movement	✓		
Abnormal signs			
Lower total score			
Neonatal Intensive Care Unit			
Network Neurobehavioral Scale			
[36]	✓		
Suboptimal excitability	✓		
Suboptimal regulation	✓	✓	✓
Suboptimal arousal			
Suboptimal lethargy			
General Movements Assessment [53]	✓		✓
Trajectory			

3.5. Recommendations for early neurobehavioural assessment for LP infants

We recommend using a combination of the GMA with a neurobehavioural assessment tool such as the HNNE or the NNNS. The optimal timing would be at a corrected age of term-equivalent, and at 3 months corrected age for the fidgety GMs. The GMA strength is assessing the overall integrity of the central nervous system, whereas the neurobehavioural examination focuses on specific strengths and vulnerabilities. The HNNE was designed to be easily administered in clinical settings and requires no formal training. It is ideal for use in routine clinical practice to screen MLP infants prior to discharge from hospital or at early follow-up appointment near term age. The NNNS was designed for research purposes and is a more comprehensive assessment. This has advantages in that it provides greater detail across a number of neurobehavioural domains and has excellent reliability but does require formal training.

4. Future directions of research

There is more to be learnt about the underlying brain structure–-function relationships of children born LP. Recent evidence points to brain alterations associated with LP birth, and emerging evidence suggests that these alterations are associated with poorer neurodevelopment in early childhood. There is a need to replicate these findings in larger cohorts, and to focus efforts on identifying predictors of brain alterations and interventions that can modify outcomes. It is essential to follow these LP cohorts into later childhood, with neuroimaging, to see whether the alterations noted at term-equivalent persist into later childhood. Such studies would enable us to determine whether the differences in brain structure at term equivalent persists or improves with time. In addition, it would be vital to assess relationships between early neuroimaging and school-age neurodevelopment to determine the clinical significance of structural differences reported at term equivalent. This information will be critical to determine the clinical utility of brain MRI in LP children.

It is also encouraging to see the potential of early standardised neurobehavioural assessments in identifying LP children at high risk of neurodevelopmental deficits. An advantage of neurobehavioural assessment is the feasibility of translation to clinical practice, in that many clinicians already working with LP babies can be trained to perform these assessments to assist in their day-to-day clinical practice.

5. Conclusions

Late preterm children are at higher risk of developmental problems in early childhood than those born full term. Whether this is a result of

ex-utero growth in the LP period, or the underlying reason for LP delivery, is yet to be determined. The insights into underlying brain alterations from neuroimaging, as well as aberrant early neurobehaviour, help us to understand the mechanisms and early predictors of poor outcomes in LP children.

Conflicts of interest

None declared.

Funding sources

This work is supported by the following grants from the Australian National Health and Medical Research Council: project grants 1028822 and 1034516, Centre os Research Excellence grant 1060733, Career Development Fellowship grant (1141354 to Dr Cheong, 1085754 to Dr Thompson, 1108714 to Dr Spittle). This study was also supported by the Victorian Government's Operational Infrastructure Support Program.

Practice points

- Late preterm children have on average smaller and less mature brains than term children, but overall prevalence of major brain injury is low.
- Brain alterations seen on MRI are associated with poorer neurodevelopment at 2 years.
- Neonatal neurobehaviour is less optimal in LP infants than in term infants.
- Suboptimal neurobehaviour in LP infants is associated with poorer neurodevelopment at 2 years.

Research directions

- Determine whether differences in brain structure persist or improve with time.
- Assess relationships between early neuroimaging and neurobehaviour with school-age neurodevelopment.
- Identify risk factors that are associated with brain structure and abnormal neurobehaviour in LP children.
- Establish clinical utility of neonatal neuroimaging and neurobehaviour.

References

[1] Cheong JL, Doyle LW, Burnett AC, et al. Association between moderate and late preterm birth and neurodevelopment and social–emotional development at age 2 years. JAMA Pediatr 2017;171:e164805.
[2] Zwicker JG, Missiuna C, Harris SR, Boyd LA. Brain activation of children with Developmental Coordination Disorder is different than peers. Pediatrics 2010;126:e678–86.
[3] Woythaler M, McCormick MC, Mao WY, Smith VC. Late preterm infants and neurodevelopmental outcomes at kindergarten. Pediatrics 2015;136:424–31.
[4] Chyi LJ, Lee HC, Hintz SR, Gould JB, Sutcliffe TL. School outcomes of late preterm infants: special needs and challenges for infants born at 32 to 36 weeks gestation. J Pediatr 2008;153:25–31.
[5] Johnson S. Cognitive and behavioural outcomes following very preterm birth. Semin Fetal Neonatal Med 2007;12:363–73.
[6] Kinney HC. The near-term (late preterm) human brain and risk for periventricular leukomalacia: a review. Semin Perinatol 2006;30:81–8.
[7] Smyser CD, Snyder AZ, Neil JJ. Functional connectivity MRI in infants: exploration of the functional organization of the developing brain. Neuroimage 2011;56:1437–52.
[8] Reinis S, Goldman JM. The development of the brain: biological and functional perspectives. Springfield, IL: Charles C. Thomas; 1980.
[9] Pape KE, Blackwell RJ, Cusick G, et al. Ultrasound detection of brain damage in preterm infants. Lancet 1979;1:1261–4.
[10] Costeloe KL, Hennessy EM, Haider S, Stacey F, Marlow N, Draper ES. Short term outcomes after extreme preterm birth in England: comparison of two birth cohorts in 1995 and 2006 (the EPICure studies). BMJ 2012;345. e7976.
[11] de Vries LS, Benders MJ, Groenendaal F. Imaging the premature brain: ultrasound or MRI? Neuroradiology 2013;55(Suppl 2):13–22.
[12] Fumagalli M, Ramenghi LA, De Carli A, et al. Cranial ultrasound findings in late preterm infants and correlation with perinatal risk factors. Ital J Pediatr 2015;41:65.
[13] Ballardini E, Tarocco A, Baldan A, Antoniazzi E, Garani G, Borgna-Pignatti C. Universal cranial ultrasound screening in preterm infants with gestational age 33–6 weeks. A retrospective analysis of 724 newborns. Pediatr Neurol 2014;51:790–4.
[14] Anderson PJ, Cheong JL, Thompson DK. The predictive validity of neonatal MRI for neurodevelopmental outcome in very preterm children. Semin Perinatol 2015;39:147–58.
[15] Haynes RL, Sleeper LA, Volpe JJ, Kinney HC. Neuropathologic studies of the encephalopathy of prematurity in the late preterm infant. Clin Perinatol 2013;40:707–22.
[16] Walsh JM, Doyle LW, Anderson PJ, Lee KJ, Cheong JL. Moderate and late preterm birth: effect on brain size and maturation at term-equivalent age. Radiology 2014;273:232–40.
[17] Nguyen The Tich S, Anderson PJ, Shimony JS, Hunt RW, Doyle LW, Inder TE. A novel quantitative simple brain metric using MR imaging for preterm infants. Am J Neuroradiol 2009;30:125–31.
[18] Brumbaugh JE, Conrad AL, Lee JK, et al. Altered brain function, structure, and developmental trajectory in children born late preterm. Pediatr Res 2016;80:197–203.
[19] Rogers CE, Barch DM, Sylvester CM, et al. Altered gray matter volume and school age anxiety in children born late preterm. J Pediatr 2014;165:928–35.
[20] Alexander B, Kelly CE, Adamson C, et al. Changes in neonatal regional brain volume associated with preterm birth and perinatal factors. Neuroimage 2018 Jul 21. pii: S1053-8119(18)30636-0.
[21] Pineda RG, Neil J, Dierker D, et al. Alterations in brain structure and neurodevelopmental outcome in preterm infants hospitalized in different neonatal intensive care unit environments. J Pediatr 2014;164:52–60. e2.
[22] Pineda R, Guth R, Herring A, Reynolds L, Oberle S, Smith J. Enhancing sensory experiences for very preterm infants in the NICU: an integrative review. J Perinatol 2017;37:323–32.
[23] Munakata S, Okada T, Okahashi A, et al. Gray matter volumetric MRI differences late-preterm and term infants. Brain Dev 2013;35:10–6.
[24] Kelly CE, Cheong JL, Gabra Fam L, et al. Moderate and late preterm infants exhibit widespread brain white matter microstructure alterations at term-equivalent age relative to term-born controls. Brain Imaging Behav 2016;10:41–9.
[25] Degnan AJ, Wisnowski JL, Choi S, et al. Altered structural and functional connectivity in late preterm preadolescence: an anatomic seed-based study of resting state networks related to the posteromedial and lateral parietal cortex. PLoS One 2015;10:e0130686.
[26] Degnan AJ, Wisnowski JL, Choi S, et al. Alterations of resting state networks and structural connectivity in relation to the prefrontal and anterior cingulate cortices in late prematurity. Neuroreport 2015;26:22–6.
[27] Kim DJ, Davis EP, Sandman CA, et al. Longer gestation is associated with more efficient brain networks in preadolescent children. Neuroimage 2014;100:619–27.
[28] Batalle D, Hughes EJ, Zhang H, et al. Early development of structural networks and the impact of prematurity on brain connectivity. Neuroimage 2017;149:379–92.
[29] Wu X, Wei L, Wang N, et al. Frequency of spontaneous BOLD signal differences between moderate and late preterm newborns and term newborns. Neurotox Res 2016;30:539–51.
[30] Cheong JL, Thompson DK, Spittle AJ, et al. Brain volumes at term-equivalent age are associated with 2-year neurodevelopment in moderate and late preterm children. J Pediatr 2016;174:91–7. e1.
[31] El-Dib M, Massaro AN, Glass P, Aly H. Neurodevelopmental assessment of the newborn: an opportunity for prediction of outcome. Brain Dev 2011;33:95–105.
[32] Brown N, Spittle A. Neurobehavioral evaluation in the preterm and term infant. Curr Pediatr Rev 2014;10:65–72.
[33] Brown NC, Inder TE, Bear MJ, Hunt RW, Anderson PJ, Doyle LW. Neurobehavior at term and white and gray matter abnormalities in very preterm infants. J Pediatr 2009;155:32–8. 8.e1.
[34] Pineda RG, Tjoeng TH, Vavasseur C, Kidokoro H, Neil JJ, Inder T. Patterns of altered neurobehavior in preterm infants within the neonatal intensive care unit. J Pediatr 2013;162:470–476.e1.
[35] Eeles AL, Walsh JM, Olsen JE, et al. Continuum of neurobehaviour and its associations with brain MRI in infants born preterm. BMJ Paediatr Open 2017;1:e000136.
[36] Spittle AJ, Walsh JM, Potter C, et al. Neurobehaviour at term-equivalent age and neurodevelopmental outcomes at 2 years in infants born moderate-to-late preterm. Dev Med Child Neurol 2017;59:207–15.
[37] Noble Y, Boyd R. Neonatal assessments for the preterm infant up to 4 months corrected age: a systematic review. Dev Med Child Neurol 2012;54:129–39.
[38] Dubowitz LM, Dubowitz V, Mercuri E. The neurological assessment of the preterm and full-term newborn infant. second ed. Cambridge: MacKeith Press; 1999.
[39] Lester BM, Tronick EZ, Brazelton TB. The neonatal intensive care unit network neurobehavioral scale procedures. Pediatrics 2004;113:641–67.
[40] Einspieler C, Prechtl HFR, Bos AF, Ferrari F, Cioni G. Prechtl's method on the qualitative assessment of general movements in preterm, term and young infants. first ed. Cambridge: MacKeith Press; 2004.
[41] Spittle AJ, Walsh J, Olsen JE, et al. Neurobehaviour and neurological development in the first month after birth for infants born between 32–42 weeks' gestation. Early Hum Dev 2016;96:7–14.
[42] Ricci D, Romeo DM, Haataja L, et al. Neurological examination of preterm infants at term equivalent age. Early Hum Dev 2008;84:751–61.
[43] Romeo DM, Luciano R, Corsello M, et al. Neonatal neurological examination of late preterm babies. Early Hum Dev 2013;89:537–45.

[44] Romeo DM, Ricci D, Brogna C, et al. Neurological examination of late-preterm infants at term age. Eur J Paediatr Neurol 2011;15:353–60.
[45] Liu J, Bann C, Lester B, et al. Neonatal neurobehavior predicts medical and behavioral outcome. Pediatrics 2010;125:e90–8.
[46] Bosanquet M, Copeland L, Ware R, Boyd R. A systematic review of tests to predict cerebral palsy in young children. Dev Med Child Neurol 2013;55:418–26.
[47] Spittle AJ, Spencer-Smith MM, Cheong JL, et al. General movements in very preterm children and neurodevelopment at 2 and 4 years. Pediatrics 2013;132:e452–8.
[48] Spittle AJ, Boyd RN, Inder TE, Doyle LW. Predicting motor development in very preterm infants at 12 months' corrected age: the role of qualitative magnetic resonance imaging and general movements assessments. Pediatrics 2009;123:512–7.
[49] Olsen JE, Brown NC, Eeles AL, et al. Early general movements and brain magnetic resonance imaging at term-equivalent age in infants born < 30 weeks' gestation. Early Hum Dev 2016;101:63–8.
[50] Olsen JE, Brown NC, Eeles AL, et al. Trajectories of general movements from birth to term-equivalent age in infants born < 30 weeks' gestation. Early Hum Dev 2015;91:683–8.
[51] Guzzetta A, Belmonti V, Battini R, Boldrini A, Paolicelli PB, Cioni G. Does the assessment of general movements without video observation reliably predict neurological outcome? Eur J Paediatr Neurol 2007;11:362–7.
[52] Bruggink JL, Van Braeckel KN, Bos AF. The early motor repertoire of children born preterm is associated with intelligence at school age. Pediatrics 2010;125:e1356–63.
[53] Sustersic B, Sustar K, Paro-Panjan D. General movements of preterm infants in relation to their motor competence between 5 and 6 years. Eur J Paediatr Neurol 2012;16:724–9.