Neuroscience meets nurture: the challenges of prematurity and the critical role of family-centred and developmental care as a key part of the neuroprotection care bundle

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What is known about this topic?

1. Preterm survival rates at the lowest gestational ages have improved.
2. Preterm infants spend their most vulnerable period of brain development on the NICU, largely in the absence of positive maternal influences.
3. Severe neurological disability is reducing but morbidity related to prematurity continues to present a global challenge.

What this study adds:

1. Several drug and cell-based neuroprotective therapies are being intensely studied but require more clinical research.
2. Family centred and developmental care therapies promote parent-infant interaction and enhance the preterm experience with the potential to improve neurodevelopmental outcomes.

ABSTRACT:

Advances in neonatal-perinatal medicine have resulted in increased survival at lower gestations. Although the incidence of germinal matrix haemorrhage-intraventricular haemorrhage (GMH-IVH) and cystic periventricular leukomalacia (PVL) are reducing, a new phenotype of preterm brain injury has emerged consisting of a combination of destructive and dysmaturational effects. Consequently, severe neurological disability is reported at a lower rate than previously, but the overall morbidity associated with premature birth continues to present a large global burden and contributes significantly to increased financial costs to health systems and families. In this review, we examine the developmental milestones of fetal brain development and how preterm birth can disrupt this trajectory. We review common morbidities associated with premature birth today. Although drug and cell-based neuroprotective therapies for the preterm brain are under intense study, we outline basic, sustainable and effective non-medical, family-centred and developmental care strategies which have the potential to improve neurodevelopmental outcomes for this population and need to be considered part of the future neuroprotection care bundle.

INTRODUCTION

Despite advances in medical knowledge and techniques, prematurity and its sequelae continue to present a significant global challenge.[1] Here we review the burden of prematurity, preterm brain development and injury, commonly associated neurodevelopmental morbidities, and focus on the evidence in support of developmental and family centred care practices to enhance preterm brain development and neurodevelopmental outcomes.

PRETERM BIRTH AND SURVIVAL

Nearly fifteen million babies are born preterm every year (WHO definition <37 completed weeks gestation[2]). The ten countries with the highest rates of prematurity (mainly sub-Saharan Africa and South Asia) account for 60% of all preterm births worldwide. Although rates are highest on average for low-income countries (11.8%), followed by lower-middle-income countries (11.3%) and lowest for upper-middle- and high-income countries (9.4% and 9.3%), relatively high preterm birth rates are seen in many individual high-income countries where they contribute substantially to neonatal mortality and morbidity.[1] [Fig 1]

For infants born at 22+0–25+6 weeks in the UK, survival to discharge has continued to improve over the decades from 40% in 1995, to 66% in 2014.[3] Several international studies have similarly indicated an incremental improvement in survival for the most premature babies over the last 1-2 decades.[4 5 6 7] The largest changes in outcome are at the lowest gestational ages. At 22 weeks GA, recent cohort studies from the US, UK, Sweden and Germany indicate that approximately 30% of live-born babies who receive active treatment survive to discharge.[6]

PRETERM BRAIN DEVELOPMENT

The human central nervous system (CNS) develops with a pattern similar to all mammals, beginning as a simple neural tube and gradually developing features through hugely complex and strictly regulated processes. The growth rate in the human CNS is higher than any other organ from the 4th postconceptional week (PCW) to the 3rd postnatal year.[8] The association areas of the cerebral neocortex develop more slowly, and the gestation period and childhood are much longer compared to other mammals. This period of dependency and the prolonged developmental course allows, more than any other species, the environment to shape the development of cognition, social and emotional factors. In addition, the developing human brain has larger proliferative areas and diverse subtypes of neural and progenitor cells that lead to increased brain expansion, especially of the neocortex.[8]

Fetal development is the most important period for neurogenetic events, with regards to number of neurons (proliferation), their molecular diversity (molecular specification), allocation

in the cortex (migration), phenotype differentiation (dendritogenesis), and is a time for the growth of axons (axonogenesis) and functional contacts (synaptogenesis).[9] The subplate zone of the telencephalon plays a pivotal role in the development of the human brain and is the most prominent transient compartment of the fetal cortex. It is the major site of synaptogenesis and neuron maturation and is a site for increasing the number of associative and thalamocortical pathways in the human neocortex.[9] Most developmental processes extend into the post-natal period, especially processes associated with interneuron connectivity.[10] Each of these cellular processes may be vulnerable to environmental influences, and their impairment may disrupt brain growth.[11] [12] [Fig 2]

The third trimester is a critical period during which global and regional brain volume increases three to fourfold. The general architecture of the human brain is achieved during the first 6 months of fetal life, mostly driven by genetic influences, which are then silenced in the third trimester [13], when environmental factors, uterine or in the NICU [14] [15] [16] [17]strongly influence the last phases of prenatal and early postnatal brain development.[18] Prematurity is one of many biological or environmental insults that can push the trajectory of the developing brain to an atypical path, with the resultant increased prevalence of neurodevelopmental and neuropsychiatric disorders.[10]

SENSORY DEVELOPMENT OF THE FETUS

The sensory systems of the fetus become functional in the following sequence during early development: tactile > vestibular > chemical > auditory > visual. As a result, the various sensory modalities have markedly different developmental histories at the time of birth.[19] The basic structure of the eyes, ears and olfactory bulb develop early in gestation. Some of the primary receptors for touch, position and motion also develop early. The development of touch starts at around 8 PCW, initially beginning with sensory receptor development in the face, mostly on the lips and nose. Taste buds begin to emerge at 8 PCW and at 13-15 PCW, the fetus has similar taste buds to adults. Smell develops around the same time that the fetus has taste function. The neural architecture of each sensory system is built at 22-40 weeks gestation and further develops in the neonatal period. The hearing system is fully developed at 20 PCW. At 23 PCW, an unborn baby can respond to loud noises. A newborn baby's eyes are susceptible to bright light but are short-sighted at only 8 to 12 inches in front of their face.

Adverse neonatal experiences can alter brain development and subsequent behaviour in preterm infants.[20] [21] They are exposed to many stimuli from which they would have been protected in-utero, including the NICU environmental and its related stressful events. Calming experiences are few, including lower levels of maternal oxytocin. The nature of delivery of

sensory experience received in the NICU can over stimulate later developing sensory systems (auditory and visual) and under stimulate earlier developing systems (tactile and vestibular), while also reducing the amount and availability of intersensory redundancy.[19] The interplay of these sensory experiences and its influence on future neurodevelopment is not yet well understood.

BRAIN MRI ABNORMALITIES ASSOCIATED WITH PREMATURITY

Survival at lower gestations has seen the emergence of new phenotypes of preterm brain injury. With the incidence of germinal matrix haemorrhage-intraventricular haemorrhage (GMH-IVH) and cystic periventricular leukomalacia (PVL) reducing,[22] a more diffuse pattern of white matter injury, characterised by loss of oligodendrocyte precursors, is more frequently seen. Punctate white matter lesions (PWML) are the most common MRI abnormality in preterms imaged at term equivalent age and are associated with an increased risk for poor motor outcome.[23] [Fig 3]

The term "encephalopathy of prematurity" describes the combination of destructive and dysmaturational effects leading to abnormal white matter (WM) and grey matter (GM) development.[24] Neonatal MRI has shown a signature pattern of preterm birth that includes alterations in white and grey matter microstructure, impaired cortical folding and disturbances in regional brain growth. These structural changes reflect a dysconnectivity of neural networks and atypical development of cortical and deep grey matter structures.[25] [10] While MRI has advanced our understanding of preterm brain injury, predicting neurodevelopmental outcome based on lesions other than PVL and haemorrhagic periventricular infarction (HPI), is still elusive.[26]

Brain growth: Although brain growth is rapid between 25 and 40 weeks in a preterm baby on the NICU, the growth trajectory is less than in a healthy fetus over the same duration. MR imaging studies of preterm infants have identified reduced cortical [Fig 4] and subcortical grey matter volumes[27] diminished cerebellar volumes[28] and alterations in thalamo-cortical development at term-equivalent age.[29] The long-term effects of prematurity are observed by alterations in WM and GM volumes seen in adolescence.[30]

Microstructural brain development of white and grey matter: Diffusion MRI (dMRI) has demonstrated altered WM development in preterm infants without focal lesions,[31] which is related to neurodevelopmental performance in early childhood [32] and adolescence [33]. Using dMRI to assess macrostructural connectivity[34] the organisation of structural brain networks during the preterm period has been characterised, demonstrating a relative preservation of

specific core connections at term equivalent age.[35] Of great interest, Batalle and colleagues recently demonstrated relative preservation of these specific core connections whereas regional connectivity involving thalamus, cerebellum, superior frontal lobe, cingulate gyrus and short-range cortico-cortical connections were related to the degree of prematurity. [36]

Compared to term-born infants, preterm infants at term corrected age have impaired cortical development with decreased cortical folding[29]; reduced GM volumes are associated with foetal growth restriction [37] and slower postnatal growth. [38]

Factors associated with the preterm birth signature have been elegantly reviewed by Boardman and Counsell 2020. Maternal factors associated with altered brain development include chorioamnionitis, fetal growth restriction, socioeconomic deprivation and prenatal alcohol, drug and stress exposures; fetal factors include nutrition, pain and medication and variation conferred by the genome/epigenome.[25]

NEURODEVELOPMENTAL OUTCOMES OF PRETERM INFANTS

Although rates of severe neurological disability, cerebral palsy (CP) and intellectual disability, are reduced compared to previously reported, 5-15% of very preterm survivors are still affected. Milder cognitive disabilities, learning difficulties, and behavioural problems are detected in 25-50% of preterm survivors at preschool and school age.[39 40]

Whilst the extremely preterm and very preterm infants are found to have disadvantages across all domains of development; the moderately preterm infants have more favourable developmental trajectories. [41-44] The motor, cognitive, behavioural, and psychiatric disabilities in the moderate and late preterm population, however, have a greater impact being the larger proportion of the preterm population.[41 42 45-47] An estimated 0.9 million post-neonatal survivors suffer long-term neurodevelopmental impairment with 345,000 being moderately or severely affected, presenting a large global burden.[43 48]

Impairment is often defined as a composite of neurosensory (CP, blindness, deafness) and developmental outcomes. However, there may be variation in the aspects of these outcomes included and the cut offs used for defining the developmental delay.[49] Of babies born in the UK before 27 weeks GA in 2006, 13.4% (n=77) were categorised as having a severe impairment and 11.8% (n=68) moderate impairment at three years.[40] Outcomes for most neonatal networks and national studies are similar, although differences in cohort and impairment definitions make it challenging to compare the data between countries.[48] [Fig 5]

Outcomes at school age or beyond are more valid compared to earlier assessments.[41 45 47] Male gender and lower maternal education are associated with both lower early learning composite scores and a decline in scores over time. [42] Bronchopulmonary dysplasia is found to be a crucial factor for cognitive outcome.[50]

Motor:

Motor impairments are common in the preterm population and include CP, developmental coordination disorder (DCD), and other disorders of movement and its control. CP is the most well defined and the most severe form. [41]

Prematurity is the most frequent cause of CP, with an incidence of 9.1% in adults born at 23 to 27 weeks' gestation inclusive. The spastic subtype accounts for 96% of CP in preterm infants, with 60% being spastic diplegia, and 17% spastic quadriplegia.[51]

Motor difficulties associated with DCD, although often considered "minor" can have a significant impact on the child's abilities.[41]

Cognitive:

Cognitive impairment is well recognised after extreme preterm birth but is complex and influenced by multiple processes and not easily predicted by brain injury. Limitations of the available assessments make it difficult to accurately estimate long term cognitive challenges.[51]

Cognitive scores at school age and beyond are 11 to 12 points lower in children born preterm, with mean IQ being 5 to 7 points lower than in controls. Those with executive dysfunction have difficulty in tasks such as initiating activities, organisation, flexibility in generating ideas and problem solving, working memory, inhibition, and attention problems. Weaknesses in working memory and visuo-motor integration are particular challenges in preterm survivors.[41]

Behaviour:

Approximately 40% of preterm infants have an overall atypical pattern of behaviour with respect to processing sensory stimuli, and almost 90% have a probable or definite abnormality in one or more sensory processing domains (e.g., oral, auditory, tactile, visual).[41]

Extremely preterm infants are at 4 times the risk of attention deficit hyperactivity disorder as compared to term infants with a four-fold increase in risk of autistic spectrum disorder.[52] Psychiatric disorders occur in approximately 25% of those born preterm.[41 51]

Speech and language:

Language development is seen to be more delayed than motor or cognitive abilities in early childhood. Expressive language, receptive language processing, and articulation difficulties with deficits in phonologic memory are seen at an older age.[41]

Academic achievements:

Preterm children are 2.85 times more likely than their term-born peers to receive special education and score significantly worse in arithmetic, reading, and spelling. Weaknesses in attention, executive functioning, visual-motor skills, and verbal memory in preterm children may all be contributing factors. Socioeconomic status is an important modifier of the relationship between prematurity and IQ. [41 51]

STRATEGIES TO IMPROVE OUTCOMES, AND THE CRITICAL ROLE OF FAMILY CENTRED AND DEVELOPMENTAL CARE

Medical therapies:

Optimising outcomes for premature babies starts with good obstetric care to promote fetal growth and well-being. Use of antenatal corticosteroids and magnesium sulphate are recommended for fetal neuroprotection. Attention to detail with appropriate expertise and facilities at delivery and in everyday management are essential for healthy brain development.[53] Caffeine, used for apnoea of prematurity is neuroprotective in pre-clinical models [54] and improves survival without neurodevelopmental disability.[55] Delayed cord clamping may allow improved cardiovascular transition with improved cerebral autoregulation but meta-analysis failed to demonstrate a significant benefit in major neonatal neurological morbidities.[56]

Researchers around the world are keenly focused on developing pharmacological therapies to protect the preterm brain. Disappointingly, even though erythropoietin showed neuroprotective effects in preclinical models,[57] high-dose early erythropoietin administration to extremely preterm infants did not lower the risk of severe neurodevelopmental impairment or death at 2 years of age.[58] Stem cell or exosomal therapies are particularly promising for protection, regeneration and repair of the injured developing brain. Mesenchymal Stem Cells (MSC) are attractive because of their low immunogenicity, self-renewing capacity, multi-lineage differentiation and secretome. Animal models suggest that administration of MSCs significantly reduces brain injury and post haemorrhagic hydrocephalus after IVH by reducing inflammation, gliosis and apoptosis of the immature brain.[59] [60]Administration of MSC is

possible intranasally, with stem cells migrating or "homing" to the injured regions within 2 hours; [61] this opens up great possibilities for treatment of preterm babies over the course of their stay in NICU. A recent report highlights the presence of stem cells in breast milk and the intriguing possibility that nasal breast milk might exert neuroprotective effects in preterm infants.[62] However further clinical research is needed; on recent systematic review of clinical studies, there is no evidence of benefit of stem cell- or exosome-based therapies for treatment of GMH-IVH, or any other brain injury in the preterm infant.[63]

Non-Medical therapies:

Admission to NICU has been associated with poor psychological functioning in mothers and fathers and negative parenting behaviours. The technical environment of the baby and NICU architecture may pose barriers to physical closeness.[64 65] Animal data suggests that prolonged physical separation between parent and newborn alters brain development and results in higher cortisol levels in the infants [66-70] and is associated with stress and anxiety in parents.[71]

Family-Centred and Developmental Care practices are promising therapies with the potential to enhance the preterm baby experience and ameliorate the trajectory towards preterm birth MRI signature and phenotype.

Developmental care is defined as the wide range of medical and nursing interventions that help to decrease the stress of preterm neonates in neonatal intensive care units. These interventions are designed to allow optimal neurobehavioral development of the infant. A large variety of interventions and environmental tools have been extensively studied - light and noise levels, scheduling of care according to the baby's behaviour and state of sleep, limiting painful procedures, general motor containment, quality oral feeding.

Neonatal individualised developmental care and assessment programme (NIDCAP) is an individualised approach that integrates a number of interventions and is based on the synactive theory model. NIDCAP has been developed to interact with preterm infants at levels adapted to their degree of neurological maturity. Increase in support to the infant's behavioural self-regulation has been shown to improve medical, behavioural and developmental outcomes and has a positive impact on neurophysiology and brain structure, likely due to prevention of inappropriate inputs during a highly sensitive period of brain development.[72]

Improved long-term outcomes in infant cognitive, motor and emotional functioning due to NIDCAP in the NICU has been reported up to school age. Enhanced parent confidence and

competence is also well documented. [72] Meta-analysis of studies thus far has, however, failed to show significant benefits, likely due to lack of good quality large trials.[73]

Skin-to-skin contact (SSC) and Kangaroo mother care (KMC) [Fig 6] are the two most studied, multisensorial parent interventions. A multitude of positive effects have been observed, such as supporting infant physiological stability, preventing pain, strongly promoting infant growth and neurobehavioral development, improving breastfeeding, reducing neonatal morbidities, parental anxiety, neonatal stress scores, nosocomial infections, hypothermia and length of stay.[74] [75] Earlier and longer contact provides greater benefit and studies have alluded to a dose-response relationship.[76]

SSC and KMC have been shown to confer several benefits to the preterm brain with increased brain maturation [77] improved connectivity [78], improved cerebral blood flow [79], and a positive influence on brain networks and synaptic efficacy up to adolescence.[80] KMC is also shown to increase oxytocin levels and decrease cortisol reactivity in term infants.[81] Studies elude to a lasting impact on self-regulation skills later in infancy [82], improved executive functioning at 5 and 10 years of life[83] and significant, long-lasting social and behavioural protective effects even after 20 years of the intervention.[84] Further longer-term effect studies of KMC on cognitive and motor development, socioemotional skills, and temperament are needed.[82]

Exposure to neonatal pain has been linked to impaired brain development in preterm infants [85], neonatal pain experience in animals may lead to physical damage or even death of young neurons in the brain.[86] [87] The activation of the hypothalamic-pituitary-adrenal (HPA) axis, in response to stressors during the critical periods of brain development, has been associated with many acute and long-term adverse bio-behavioural outcomes. KMC accelerates neurophysiological maturation of premature neonates [77] and reduces the HPA axis response to pain and reduced maternal care leading to typical development of the HPA axis and brain with normal cognitive functioning and behavioural outcomes.[74]

The exact biological mechanism of how KMC results in the large range of beneficial outcomes however remains largely unknown. The relatively limited sample sizes of the studies thus far, heterogeneity in strategies and outcome measures and the potential for confounding variables highlight the need for further trails with clearly defined and similar outcomes.

Breastfeeding is well known to have a range of social, emotional and health benefits for both the term and preterm infant and mother. The cognitive and developmental advantages to breastfed infants have been acknowledged in the literature as early as the 1970s.[88] The

positive impact of breastfeeding on intellectual development has subsequently been established with evidence of a lasting impact through to adulthood.[89] Improvement in cognitive development is even greater in preterm and very low birth weight infants. [90 91]

Adolescents that were breastfed in infancy have an increase in total white matter, sub-cortical grey matter and parietal lobe cortical thickness. Studies using evoked potentials suggest delayed or immature myelination of early neural pathways in formula-fed infants as compared to breastfed ones. More recently, imaging studies of preterm infants at term equivalent age demonstrate an association between higher exposure to breast milk feeding with improved microstructural properties of white matter tracts and cerebral structural connectivity. These effects had a dose-dependent relationship with breast milk exposure. [92 93]

Family-Centred Care (FCC) interventions are based on the principle of recognising the parents as integral members of the care team, who work in partnership and collaboration with healthcare professionals in the planning and delivery of their infant's care.[64]

By encouraging parental presence, FCC facilitates parent-infant closeness, including skin-to-skin contact and breastfeeding, and synchronises cortisol variation between the preterm infant and mother. Several mechanisms maybe involved in improving outcomes from parent-infant contact such as improved sleep, pain management with moderated needs for pain medication, infant touch and massage with resultant brain growth-promoting factors and oxytocin, interactive communication with the parent, positive auditory experience,[94] all enhancing neurological, neurobehavioural and neurocognitive outcomes in preterm infants.[71 95] Close physical and emotional contact between parent and preterm infant, also reduces short and long term parental stress[96] and decreases infant's cortisol levels and pain responses.[71]

EEG assessments indicate that cerebral cortical development is promoted by parent-infant interaction and brain maturation may also be accelerated, particularly in frontal brain regions, which have been shown to be involved in regulation of attention, cognition and emotion; domains known to be deficient in preterm infants.[97] Other reported benefits of FCC include reduction in length of stay, and moderate to severe bronchopulmonary dysplasia, which in itself is a strong predictor of poor neurodevelopmental outcome.[64 65]

Family Integrated Care (FIC) is a more recent concept which draws on all the essential elements of Family-Centred Care but advances it further by enabling parents to become their infant's primary caregiver and to actively participate in their care. In a recent large multi-centre randomised controlled trail, FIC significantly improved infant weight gain and parental stress

and anxiety.[98] Other centres have reported improvement in breastfeeding rates and length of stay.[99]

CONCLUSIONS:

The third trimester is a critical period of brain development. Prematurity and its related experiences can push the trajectory of the developing brain to an atypical path during this most vulnerable period, which is spent largely on the NICU, in the absence of positive maternal influences. FCC and developmental care promote parent-infant interaction and are safe and feasible in most settings and socioeconomic conditions. They have the potential to enhance the preterm baby experience and improve neurodevelopmental outcomes globally in the high-risk preterm population. These practices should be considered part of the neuroprotection care bundle and are important considerations in future clinical trials of pharmacological therapies for brain protection in preterm infants.

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REFERENCES:

1. Blencowe H, Cousens S, Chou D, et al. Born too soon: the global epidemiology of 15 million preterm births. *Reprod Health* 2013;10 Suppl 1(Suppl 1):S2. doi: 10.1186/1742-4755-10-s1-s2 [published Online First: 2014/03/15]
2. WHO: recommended definitions, terminology and format for statistical tables related to the perinatal period and use of a new certificate for cause of perinatal deaths. Modifications recommended by FIGO as amended October 14, 1976. *Acta Obstet Gynecol Scand* 1977;56(3):247-53. [published Online First: 1977/01/01]
3. Santhakumaran S, Statnikov Y, Gray D, et al. Survival of very preterm infants admitted to neonatal care in England 2008-2014: time trends and regional variation. *Arch Dis Child Fetal Neonatal Ed* 2018;103(3):F208-f15. doi: 10.1136/archdischild-2017-312748 [published Online First: 2017/09/09]
4. Younge N, Goldstein RF, Bann CM, Hintz SR, Patel RM, Smith PB, et al. Survival and Neurodevelopmental Outcomes among Periviable Infants. N Engl J Med. 2017;376(7):617-28
5. Cheong JLY, Olsen JE, Huang L, Dalziel KM, Boland RA, Burnett AC, et al. Changing consumption of resources for respiratory support and short-term outcomes in four consecutive geographical cohorts of infants born extremely preterm over 25 years since the early 1990s. BMJ Open. 2020;10(9): e037507.
6. Mactier H, Bates SE, Johnston T, et al. Perinatal management of extreme preterm birth before 27 weeks of gestation: a framework for practice. *Arch Dis Child Fetal Neonatal Ed* 2020;105(3):232-39. doi: 10.1136/archdischild-2019-318402 [published Online First: 2020/01/26]
7. Norman M, Hallberg B, Abrahamsson T, et al. Association Between Year of Birth and 1-Year Survival Among Extremely Preterm Infants in Sweden During 2004-2007 and 2014-2016. *Jama* 2019;321(12):1188-99. doi: 10.1001/jama.2019.2021 [published Online First: 2019/03/27]

8. Silbereis JC, Pochareddy S, Zhu Y, et al. The Cellular and Molecular Landscapes of the Developing Human Central Nervous System. *Neuron* 2016;89(2):248-68. doi: 10.1016/j.neuron.2015.12.008 [published Online First: 2016/01/23]
9. Kostović I. The enigmatic fetal subplate compartment forms an early tangential cortical nexus and provides the framework for construction of cortical connectivity. *Prog Neurobiol* 2020:101883. doi: 10.1016/j.pneurobio.2020.101883 [published Online First: 2020/07/14]
10. Batalle D, Edwards AD, O'Muircheartaigh J. Annual Research Review: Not just a small adult brain: understanding later neurodevelopment through imaging the neonatal brain. *J Child Psychol Psychiatry* 2018;59(4):350-71. doi: 10.1111/jcpp.12838 [published Online First: 2017/11/07]
11. Schneider J, Miller SP. Preterm brain Injury: White matter injury. *Handb Clin Neurol* 2019;162:155-72. doi: 10.1016/b978-0-444-64029-1.00007-2 [published Online First: 2019/07/22]
12. Kidokoro H, Anderson PJ, Doyle LW, et al. Brain injury and altered brain growth in preterm infants: predictors and prognosis. *Pediatrics* 2014;134(2):e444-53. doi: 10.1542/peds.2013-2336 [published Online First: 2014/07/30]
13. Pletikos M, Sousa AM, Sedmak G, Meyer KA, Zhu Y, Cheng F, et al. Temporal specification and bilaterality of human neocortical topographic gene expression. Neuron. 2014;81(2):321-32
14. Kapellou O, Counsell SJ, Kennea N, et al. Abnormal cortical development after premature birth shown by altered allometric scaling of brain growth. PLoS Med. 2006;3(8):e265
15. Stoll BJ, Hansen NI, Adams-Chapman I, et al. Neurodevelopmental and growth impairment among extremely low-birth weight infants with neonatal infection. JAMA. 2004; 292(19):2357–2365
16. Shah DK, Doyle LW, Anderson PJ, et al. Adverse neurodevelopment in preterm infants with postnatal sepsis or necrotizing enterocolitis is mediated by white matter abnormalities on magnetic resonance imaging at term. J Pediatr. 2008;153(2):170–175, e1
17. Short EJ, Klein NK, Lewis BA, et al. Cognitive and academic consequences of bronchopulmonary dysplasia and very low birth weight: 8-year-old outcomes. Pediatrics. 2003;112(5). Available at: www.pediatrics. org/cgi/content/full/112/5/e359
18. Vasung L, Abaci Turk E, Ferradal SL, et al. Exploring early human brain development with structural and physiological neuroimaging. *Neuroimage* 2019;187:226-54. doi: 10.1016/j.neuroimage.2018.07.041 [published Online First: 2018/07/25]
19. Lickliter R. The integrated development of sensory organization. *Clin Perinatol* 2011;38(4):591-603. doi: 10.1016/j.clp.2011.08.007 [published Online First: 2011/11/24]
20. McGowan EC, Vohr BR. Impact of Nonmedical Factors on Neurobehavior and Language Outcomes of Preterm Infants. Neoreviews. 2019;20(7):e372-e384.
21. Cheong JLY, Burnett AC, Treyvaud K, Spittle AJ. Early environment and long-term outcomes of preterm infants. J Neural Transm (Vienna). 2020;127(1):1-8.
22. Groenendaal F, Termote JU, van der Heide-Jalving M, et al. Complications affecting preterm neonates from 1991 to 2006: what have we gained? *Acta Paediatr* 2010;99(3):354-8. doi: 10.1111/j.1651-2227.2009.01648.x [published Online First: 2010/01/13]
23. Tusor N, Benders MJ, Counsell SJ, et al. Punctate White Matter Lesions Associated With Altered Brain Development And Adverse Motor Outcome In Preterm Infants. *Sci Rep* 2017;7(1):13250. doi: 10.1038/s41598-017-13753-x [published Online First: 2017/10/19]
24. Volpe JJ. The encephalopathy of prematurity--brain injury and impaired brain development inextricably intertwined. *Semin Pediatr Neurol* 2009;16(4):167-78. doi: 10.1016/j.spen.2009.09.005 [published Online First: 2009/12/01]
25. Boardman JP, Counsell SJ. Invited Review: Factors associated with atypical brain development in preterm infants: insights from magnetic resonance imaging. *Neuropathol Appl Neurobiol* 2020;46(5):413-21. doi: 10.1111/nan.12589 [published Online First: 2019/11/21]

26. Arulkumaran S, Tusor N, Chew A, et al. MRI Findings at Term-Corrected Age and Neurodevelopmental Outcomes in a Large Cohort of Very Preterm Infants. *AJNR Am J Neuroradiol* 2020;41(8):1509-16. doi: 10.3174/ajnr.A6666 [published Online First: 2020/08/17]
27. Padilla N, Alexandrou G, Blennow M, et al. Brain Growth Gains and Losses in Extremely Preterm Infants at Term. *Cereb Cortex* 2015;25(7):1897-905. doi: 10.1093/cercor/bht431 [published Online First: 2014/02/04]
28. Limperopoulos C, Chilingaryan G, Guizard N, et al. Cerebellar injury in the premature infant is associated with impaired growth of specific cerebral regions. *Pediatr Res* 2010;68(2):145-50. doi: 10.1203/PDR.0b013e3181e1d032 [published Online First: 2010/04/15]
29. Ball G, Boardman JP, Aljabar P, et al. The influence of preterm birth on the developing thalamocortical connectome. *Cortex* 2013;49(6):1711-21. doi: 10.1016/j.cortex.2012.07.006 [published Online First: 2012/09/11]
30. Nosarti C, Giouroukou E, Healy E, et al. Grey and white matter distribution in very preterm adolescents mediates neurodevelopmental outcome. *Brain* 2008;131(Pt 1):205-17. doi: 10.1093/brain/awm282 [published Online First: 2007/12/07]
31. Anjari M, Srinivasan L, Allsop JM, et al. Diffusion tensor imaging with tract-based spatial statistics reveals local white matter abnormalities in preterm infants. *Neuroimage* 2007;35(3):1021-7. doi: 10.1016/j.neuroimage.2007.01.035 [published Online First: 2007/03/09]
32. Ball G, Pazderova L, Chew A, et al. Thalamocortical Connectivity Predicts Cognition in Children Born Preterm. *Cereb Cortex* 2015;25(11):4310-8. doi: 10.1093/cercor/bhu331 [published Online First: 2015/01/18]
33. Groeschel S, Tournier JD, Northam GB, et al. Identification and interpretation of microstructural abnormalities in motor pathways in adolescents born preterm. *Neuroimage* 2014;87:209-19. doi: 10.1016/j.neuroimage.2013.10.034 [published Online First: 2013/11/05]
34. Brown CJ, Miller SP, Booth BG, et al. Structural network analysis of brain development in young preterm neonates. *Neuroimage* 2014;101:667-80. doi: 10.1016/j.neuroimage.2014.07.030 [published Online First: 2014/07/31]
35. Ball G, Aljabar P, Zebari S, et al. Rich-club organization of the newborn human brain. *Proc Natl Acad Sci U S A* 2014;111(20):7456-61. doi: 10.1073/pnas.1324118111 [published Online First: 2014/05/07]
36. 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. doi: 10.1016/j.neuroimage.2017.01.065 [published Online First: 2017/02/06]
37. Miller SL, Huppi PS, Mallard C. The consequences of fetal growth restriction on brain structure and neurodevelopmental outcome. *J Physiol* 2016;594(4):807-23. doi: 10.1113/jp271402 [published Online First: 2015/11/27]
38. Vinall J, Grunau RE, Brant R, et al. Slower postnatal growth is associated with delayed cerebral cortical maturation in preterm newborns. *Sci Transl Med* 2013;5(168):168ra8. doi: 10.1126/scitranslmed.3004666 [published Online First: 2013/01/18]
39. Schneider J, Miller SP. Preterm brain Injury: White matter injury. *Handb Clin Neurol* 2019;162:155-72. doi: 10.1016/b978-0-444-64029-1.00007-2 [published Online First: 2019/07/22]
40. Moore T, Hennessy EM, Myles J, et al. Neurological and developmental outcome in extremely preterm children born in England in 1995 and 2006: the EPICure studies. *Bmj* 2012;345:e7961. doi: 10.1136/bmj.e7961 [published Online First: 2012/12/06]
41. Synnes A, Hicks M. Neurodevelopmental Outcomes of Preterm Children at School Age and Beyond. *Clin Perinatol* 2018;45(3):393-408. doi: 10.1016/j.clp.2018.05.002 [published Online First: 2018/08/27]
42. Yaari M, Mankuta D, Harel-Gadassi A, et al. Early developmental trajectories of preterm infants. *Res Dev Disabil* 2018;81:12-23. doi: 10.1016/j.ridd.2017.10.018 [published Online First: 2017/11/09]

43. Blencowe H, Lee AC, Cousens S, et al. Preterm birth-associated neurodevelopmental impairment estimates at regional and global levels for 2010. *Pediatr Res* 2013;74 Suppl 1(Suppl 1):17-34. doi: 10.1038/pr.2013.204 [published Online First: 2013/12/25]
44. Pascal A, Govaert P, Oostra A, et al. Neurodevelopmental outcome in very preterm and very-low-birthweight infants born over the past decade: a meta-analytic review. *Dev Med Child Neurol* 2018;60(4):342-55. doi: 10.1111/dmcn.13675 [published Online First: 2018/01/20]
45. Mathiasen R, Hansen BM, Andersen AM, et al. Gestational age and basic school achievements: a national follow-up study in Denmark. *Pediatrics* 2010;126(6):e1553-61. doi: 10.1542/peds.2009-0829 [published Online First: 2010/11/10]
46. MacKay DF, Smith GC, Dobbie R, et al. Gestational age at delivery and special educational need: retrospective cohort study of 407,503 schoolchildren. *PLoS Med* 2010;7(6):e1000289. doi: 10.1371/journal.pmed.1000289 [published Online First: 2010/06/15]
47. Quigley MA, Poulsen G, Boyle E, et al. Early term and late preterm birth are associated with poorer school performance at age 5 years: a cohort study. *Arch Dis Child Fetal Neonatal Ed* 2012;97(3):F167-73. doi: 10.1136/archdischild-2011-300888 [published Online First: 2012/01/05]
48. Synnes A, Luu TM, Moddemann D, et al. Determinants of developmental outcomes in a very preterm Canadian cohort. *Arch Dis Child Fetal Neonatal Ed* 2017;102(3):F235-f34. doi: 10.1136/archdischild-2016-311228 [published Online First: 2016/10/21]
49. Haslam MD, Lisonkova S, Creighton D, Church P, Yang J, Shah PS, et al. Severe Neurodevelopmental Impairment in Neonates Born Preterm: Impact of Varying Definitions in a Canadian Cohort. J Pediatr. 2018;197:75-81.e4.
50. Twilhaar ES, van Elburg RM, Oosterlaan J. Need for Further Analysis in Cognitive Outcomes of Children Born Preterm-Reply. *JAMA Pediatr* 2018;172(9):889-90. doi: 10.1001/jamapediatrics.2018.1631 [published Online First: 2018/09/06]
51. Rogers EE, Hintz SR. Early neurodevelopmental outcomes of extremely preterm infants. *Semin Perinatol* 2016;40(8):497-509. doi: 10.1053/j.semperi.2016.09.002 [published Online First: 2016/11/21]
52. Limperopoulos C, Bassan H, Sullivan NR, et al. Positive screening for autism in ex-preterm infants: prevalence and risk factors. *Pediatrics* 2008;121(4):758-65. doi: 10.1542/peds.2007-2158 [published Online First: 2008/04/03]
53. WHO Guidelines Approved by the Guidelines Review Committee. WHO Recommendations on Interventions to Improve Preterm Birth Outcomes. Geneva: World Health Organization Copyright © World Health Organization 2015. 2015.
54. Di Martino E, Bocchetta E, Tsuji S, et al. Defining a Time Window for Neuroprotection and Glia Modulation by Caffeine After Neonatal Hypoxia-Ischaemia. *Mol Neurobiol* 2020;57(5):2194-205. doi: 10.1007/s12035-020-01867-9 [published Online First: 2020/01/25]
55. Schmidt B, Roberts RS, Davis P, et al. Long-term effects of caffeine therapy for apnea of prematurity. *N Engl J Med* 2007;357(19):1893-902. doi: 10.1056/NEJMoa073679 [published Online First: 2007/11/09]
56. Fogarty M, Osborn DA, Askie L, et al. Delayed vs early umbilical cord clamping for preterm infants: a systematic review and meta-analysis. *Am J Obstet Gynecol* 2018;218(1):1-18. doi: 10.1016/j.ajog.2017.10.231 [published Online First: 2017/11/04]
57. Rangarajan V, Juul SE. Erythropoietin: emerging role of erythropoietin in neonatal neuroprotection. *Pediatr Neurol* 2014;51(4):481-8. doi: 10.1016/j.pediatrneurol.2014.06.008 [published Online First: 2014/10/01]
58. Juul SE, Comstock BA, Wadhawan R, et al. A Randomized Trial of Erythropoietin for Neuroprotection in Preterm Infants. *N Engl J Med* 2020;382(3):233-43. doi: 10.1056/NEJMoa1907423 [published Online First: 2020/01/16]
59. Ahn SY, Chang YS, Sung DK, et al. Mesenchymal stem cells prevent hydrocephalus after severe intraventricular hemorrhage. *Stroke* 2013;44(2):497-504. doi: 10.1161/strokeaha.112.679092 [published Online First: 2013/01/05]

60. Mukai T, Mori Y, Shimazu T, et al. Intravenous injection of umbilical cord-derived mesenchymal stromal cells attenuates reactive gliosis and hypomyelination in a neonatal intraventricular hemorrhage model. *Neuroscience* 2017;355:175-87. doi: 10.1016/j.neuroscience.2017.05.006 [published Online First: 2017/05/16]
61. Donega V, Nijboer CH, van Tilborg G, et al. Intranasally administered mesenchymal stem cells promote a regenerative niche for repair of neonatal ischemic brain injury. *Exp Neurol* 2014;261:53-64. doi: 10.1016/j.expneurol.2014.06.009 [published Online First: 2014/06/20]
62. Keller T, Körber F, Oberthuer A, et al. Intranasal breast milk for premature infants with severe intraventricular hemorrhage-an observation. *Eur J Pediatr* 2019;178(2):199-206. doi: 10.1007/s00431-018-3279-7 [published Online First: 2018/11/06]
63. Romantsik O, Bruschettini M, Moreira A, et al. Stem cell-based interventions for the prevention and treatment of germinal matrix-intraventricular haemorrhage in preterm infants. *Cochrane Database Syst Rev* 2019;9(9):Cd013201. doi: 10.1002/14651858.CD013201.pub2 [published Online First: 2019/09/25]
64. Yu X, Zhang J. Family-centred care for hospitalized preterm infants: A systematic review and meta-analysis. *Int J Nurs Pract* 2019;25(3):e12705. doi: 10.1111/ijn.12705 [published Online First: 2018/11/01]
65. Ortenstrand A, Westrup B, Broström EB, et al. The Stockholm Neonatal Family Centered Care Study: effects on length of stay and infant morbidity. *Pediatrics* 2010;125(2):e278-85. doi: 10.1542/peds.2009-1511 [published Online First: 2010/01/27]
66. Nishi M. Effects of Early-Life Stress on the Brain and Behaviours: Implications of Early Maternal Separation in Rodents. Int J Mol Sci. 2020;21(19).
67. Chen M, He G, Li Q. Maternal deprivation promotes hippocampal neuronal apoptosis via ERK1/2 signaling. Front Biosci (Landmark Ed). 2018;23:1923-32.
68. Bergman NJ. Birth practices: Maternal-neonate separation as a source of toxic stress. Birth Defects Res. 2019;111(15):1087-109.
69. Vázquez DM, López JF, Van Hoers H, Watson SJ, Levine S. Maternal deprivation regulates serotonin 1A and 2A receptors in the infant rat. Brain Res. 2000;855(1):76-82.
70. Feng X, Wang L, Yang S, Qin D, Wang J, Li C, et al. Maternal separation produces lasting changes in cortisol and behavior in rhesus monkeys. Proc Natl Acad Sci U S A. 2011;108(34):14312-7.
71. Flacking R, Lehtonen L, Thomson G, Axelin A, Ahlqvist S, Moran VH, et al. Closeness and separation in neonatal intensive care. Acta Paediatr. 2012;101(10):1032-7.
72. Als H, B. McAnulty G. The Newborn Individualized Developmental Care and Assessment Program (NIDCAP) with Kangaroo Mother Care (KMC): Comprehensive Care for Preterm Infants. *Current Women's Health Reviews* 2011;7(3):288-301. doi: 10.2174/157340411796355216
73. Ohlsson A, Jacobs SE. NIDCAP: a systematic review and meta-analyses of randomized controlled trials. *Pediatrics* 2013;131(3):e881-93. doi: 10.1542/peds.2012-2121 [published Online First: 2013/02/20]
74. Mooney-Leber SM, Brummelte S. Neonatal pain and reduced maternal care: Early-life stressors interacting to impact brain and behavioral development. *Neuroscience* 2017;342:21-36. doi: 10.1016/j.neuroscience.2016.05.001 [published Online First: 2016/05/12]
75. Johnston C, Campbell-Yeo M, Disher T, Benoit B, Fernandes A, Streiner D, et al. Skin-to-skin care for procedural pain in neonates. Cochrane Database Syst Rev. 2017;2(2):Cd008435.
76. Moore ER, Anderson GC, Bergman N, et al. Early skin-to-skin contact for mothers and their healthy newborn infants. *Cochrane Database Syst Rev* 2012;5(5):Cd003519. doi: 10.1002/14651858.CD003519.pub3 [published Online First: 2012/05/18]
77. Kaffashi F, Scher MS, Ludington-Hoe SM, Loparo KA. An analysis of the kangaroo care intervention using neonatal EEG complexity: a preliminary study. Clin Neurophysiol. 2013;124(2):238-46.

78. Scher MS, Ludington-Hoe S, Kaffashi F, Johnson MW, Holditch-Davis D, Loparo KA. Neurophysiologic assessment of brain maturation after an 8-week trial of skin-to-skin contact on preterm infants. Clin Neurophysiol. 2009;120(10):1812-8.
79. Korraa AA, El Nagger AA, Mohamed RA, Helmy NM. Impact of kangaroo mother care on cerebral blood flow of preterm infants. Ital J Pediatr. 2014;40:83.
80. Schneider C, Charpak N, Ruiz-Peláez JG, Tessier R. Cerebral motor function in very premature-at-birth adolescents: a brain stimulation exploration of kangaroo mother care effects. Acta Paediatr. 2012;101(10):1045-53.
81. Hardin JS, Jones NA, Mize KD, Platt M. Parent-Training with Kangaroo Care Impacts Infant Neurophysiological Development & Mother-Infant Neuroendocrine Activity. Infant Behav Dev. 2020;58:101416.
82. Akbari E, Binnoon-Erez N, Rodrigues M, Ricci A, Schneider J, Madigan S, et al. Kangaroo mother care and infant biopsychosocial outcomes in the first year: A meta-analysis. Early Hum Dev. 2018;122:22-31.
83. Feldman R, Rosenthal Z, Eidelman AI. Maternal-preterm skin-to-skin contact enhances child physiologic organization and cognitive control across the first 10 years of life. *Biol Psychiatry* 2014;75(1):56-64. doi: 10.1016/j.biopsych.2013.08.012 [published Online First: 2013/10/08]
84. Charpak N, Tessier R, Ruiz JG, et al. Twenty-year Follow-up of Kangaroo Mother Care Versus Traditional Care. *Pediatrics* 2017;139(1) doi: 10.1542/peds.2016-2063 [published Online First: 2016/12/15]
85. Brummelte S, Grunau RE, Chau V, Poskitt KJ, Brant R, Vinall J, et al. Procedural pain and brain development in premature newborns. Ann Neurol. 2012;71(3):385-96.
86. Anand KJ, Garg S, Rovnaghi CR, Narsinghani U, Bhutta AT, Hall RW. Ketamine reduces the cell death following inflammatory pain in newborn rat brain. Pediatr Res. 2007;62(3):283-90.
87. Dührsen L, Simons SH, Dzietko M, Genz K, Bendix I, Boos V, et al. Effects of repetitive exposure to pain and morphine treatment on the neonatal rat brain. Neonatology. 2013;103(1):35-43.
88. Newton N. The uniqueness of human milk. Psychological differences between breast and bottle feeding. *Am J Clin Nutr* 1971;24(8):993-1004. doi: 10.1093/ajcn/24.8.993 [published Online First: 1971/08/01]
89. Lawrence RA. Supporting Breastfeeding/Early Childhood Social and Emotion Development. In: Tremblay RE, Boivin M, Peters RDeV, eds. *Encyclopedia on Early Childhood Development* [online]. http://www.child-encyclopedia.com/breastfeeding/according-experts/supporting-breastfeedingearly-childhood-social-and-emotion. Updated March 2008.
90. Feldman R, Eidelman AI. Direct and indirect effects of breast milk on the neurobehavioral and cognitive development of premature infants. *Dev Psychobiol* 2003;43(2):109-19. doi: 10.1002/dev.10126 [published Online First: 2003/08/15]
91. Gibertoni D, Corvaglia L, Vandini S, et al. Positive effect of human milk feeding during NICU hospitalization on 24 month neurodevelopment of very low birth weight infants: an Italian cohort study. *PLoS One* 2015;10(1):e0116552. doi: 10.1371/journal.pone.0116552 [published Online First: 2015/01/16]
92. Deoni SC, Dean DC, 3rd, Piryatinsky I, et al. Breastfeeding and early white matter development: A cross-sectional study. *Neuroimage* 2013;82:77-86. doi: 10.1016/j.neuroimage.2013.05.090 [published Online First: 2013/06/01]
93. Blesa M, Sullivan G, Anblagan D, et al. Early breast milk exposure modifies brain connectivity in preterm infants. *Neuroimage* 2019;184:431-39. doi: 10.1016/j.neuroimage.2018.09.045 [published Online First: 2018/09/22]
94. McMahon E, Wintermark P, Lahav A. Auditory brain development in premature infants: the importance of early experience. *Ann N Y Acad Sci* 2012;1252:17-24. doi: 10.1111/j.1749-6632.2012.06445.x [published Online First: 2012/04/25]

95. Rahkonen P, Heinonen K, Pesonen AK, et al. Mother-child interaction is associated with neurocognitive outcome in extremely low gestational age children. *Scand J Psychol* 2014;55(4):311-8. doi: 10.1111/sjop.12133 [published Online First: 2014/05/16]
96. Sabnis A, Fojo S, Nayak SS, et al. Reducing parental trauma and stress in neonatal intensive care: systematic review and meta-analysis of hospital interventions. *J Perinatol* 2019;39(3):375-86. doi: 10.1038/s41372-018-0310-9 [published Online First: 2019/01/20]
97. Myers MM, Grieve PG, Stark RI, et al. Family Nurture Intervention in preterm infants alters frontal cortical functional connectivity assessed by EEG coherence. *Acta Paediatr* 2015;104(7):670-7. doi: 10.1111/apa.13007 [published Online First: 2015/03/17]
98. O'Brien K, Robson K, Bracht M, et al. Effectiveness of Family Integrated Care in neonatal intensive care units on infant and parent outcomes: a multicentre, multinational, cluster-randomised controlled trial. *Lancet Child Adolesc Health* 2018;2(4):245-54. doi: 10.1016/s2352-4642(18)30039-7 [published Online First: 2018/09/01]
99. Young A, McKechnie L, Harrison CM. Family integrated care: what's all the fuss about? *Arch Dis Child Fetal Neonatal Ed* 2019;104(2):F118-f19. doi: 10.1136/archdischild-2018-315307 [published Online First: 2018/07/08]