Neuroscience meets nurture: 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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ABSTRACT

Advances in neonatal–perinatal medicine have resulted in increased survival at lower gestations. Although the incidence of germinal matrix haemorrhage-intraventricular haemorrhage and cystic periventricular leucomalacia is 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-based 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. 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 15 million babies are born preterm every year (WHO definition <37 completed weeks' gestation). The 10 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-income 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] (figure 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.[2] Several international studies have similarly indicated an incremental improvement in survival for the most premature babies over the last one to two decades.[3–5] The largest changes in outcome are at the lowest gestational ages (GAs). At 22 weeks' GA, recent cohort studies from the USA, UK, Sweden and Germany indicate that approximately 30% of live-born babies who receive active treatment survive to discharge.[5]

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.[6] The association areas of the cerebral neocortex develop more slowly, and the gestation period and childhood are much longer compared with 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.[6]

Fetal development is the most important period for neurogenetic events, with regard 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).[7] 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.[7] Most developmental processes extend into the postnatal period, especially processes associated

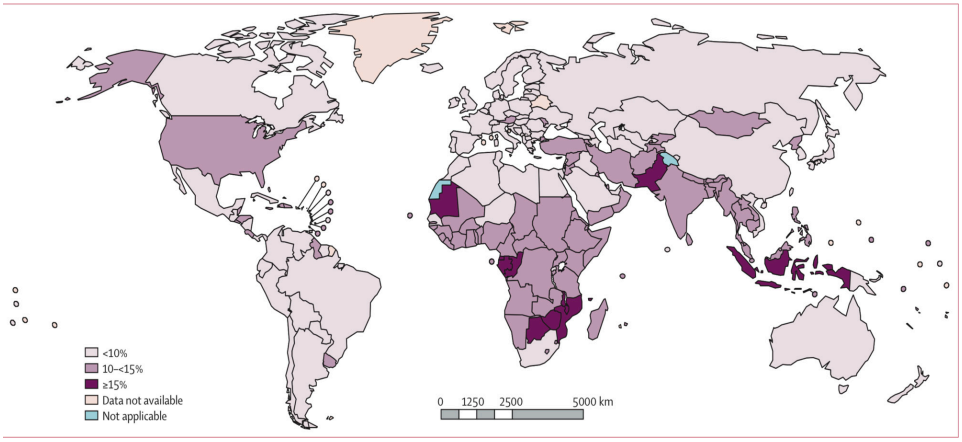

Figure 1 Estimated preterm birth rates by country for the year 2010. Source: Blencowe *et al*, Lancet 2012.

with interneuron connectivity.[8] Each of these cellular processes may be vulnerable to environmental influences, and their impairment may disrupt brain growth[9] (figure 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,[10] when environmental factors, uterine or in the neonatal intensive care unit (NICU)[11 12] strongly influence the last phases of prenatal and early postnatal brain development.[13] 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.[8]

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.[14] The basic structure of the eyes, ears and olfactory bulb develops 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.

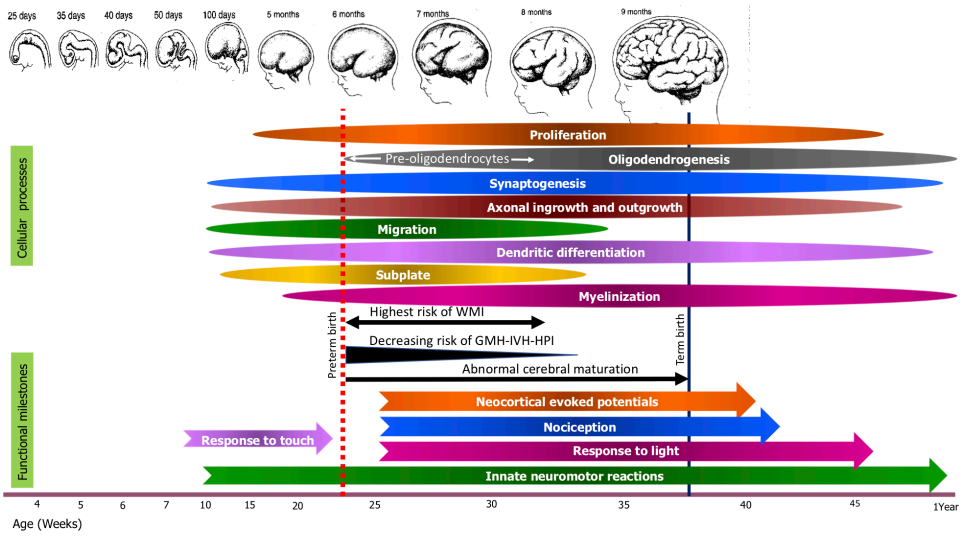

Figure 2 Figure summarising some key cellular processes in the developing prefrontal cortex and functional milestones. Illustrations in the top panel show the gross anatomical features of the developing prenatal brain. The schematic below details the approximate timing and sequence of key cellular processes and developmental milestones, indicating the peak developmental period in which each feature is acquired. Note the predominance of axonal growth, dendritic differentiation and synaptogenesis during mid-fetal and beginning of the late fetal period. Proliferation of neurons within the subplate is hypothetical during this period, but proliferation of glia continues. Note that after 34 PCW, there is dissolution of the subplate with presence of subplate remnant in the neonatal period. The period of highest risk for WMI between 23 and 32 weeks' gestation coincides with the predominance of pre-oligodendrocytes in the WM and constitutes a developmental window of enhanced susceptibility. Risk of GMH-IVH-HPI decreases by 32 weeks but abnormal cortical maturation continues until term age. The lower half of the figure shows development of functional milestones and acquisition of key sensorimotor responses. Figure adapted from Silbereis and Kostovic. GMH-IVH, germinal matrix haemorrhage-intraventricular haemorrhage; HPI, haemorrhagic periventricular infarction; PCW, postconceptional week; WM, white matter; WMI, white matter injury.

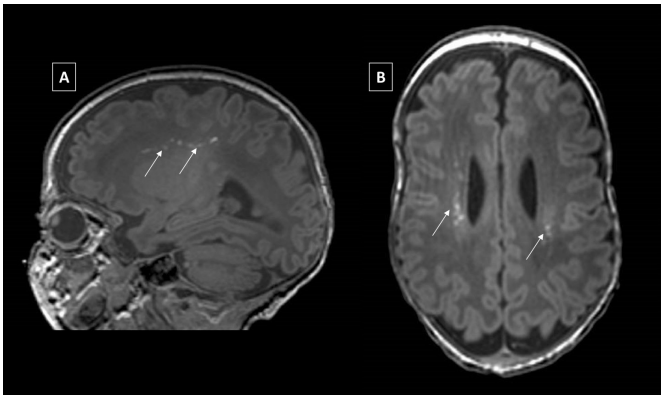

Figure 3 MRI images—preterm infant. Punctate white matter lesions (PWMLs) in a preterm infant born at 32 weeks+3 days and imaged at 40 weeks+5 days in the sagittal (A) and high axial plane (B). PWMLs are small areas of white matter injury and are the most common lesion type seen on MRI in ex-preterm babies imaged at term. PWMLs are typically defined as small foci of high T1 signal in the white matter, less often visualised on T2 sequences. PWMLs detected on a single MRI at term-equivalent age without other focal lesions or injuries in the grey matter have been associated with abnormal neuroanatomical development and adverse motor outcome at 20 months.

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 8–12 inches in front of their face.

Adverse neonatal experiences can alter brain development and subsequent behaviour in preterm infants.[15 16] They are exposed to many stimuli from which they would have been protected in utero, including the NICU environment 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 overstimulate later developing sensory systems (auditory and visual) and understimulate earlier developing systems (tactile and vestibular), while also reducing the amount and availability of intersensory redundancy.[14] 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 leucomalacia (PVL) reducing,[17] a more diffuse pattern of white matter (WM) injury, characterised by loss of oligodendrocyte precursors, is more frequently seen. Punctate WM lesions are the most common MRI abnormality in preterms imaged at term-equivalent age and are associated with an increased risk of poor motor outcome[18] (figure 3).

The term 'encephalopathy of prematurity' describes the combination of destructive and dysmaturational effects leading to abnormal WM and grey matter (GM) development.[19] Neonatal MRI has shown a signature pattern of preterm birth that includes alterations in WM and GM 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 GM structures.[8 20]

While MRI has advanced our understanding of preterm brain injury, predicting neurodevelopmental outcome based on lesions other than PVL and haemorrhagic periventricular infarction is still elusive.[21]

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. MRI studies of preterm infants have identified reduced cortical (figure 4) and subcortical GM volumes[22] diminished cerebellar volumes[23] and alterations in thalamocortical development at term-equivalent age.[24] The long-term effects of prematurity are observed by alterations in WM and GM volumes seen in adolescence.[25]

Microstructural brain development of WM and GM

Diffusion MRI (dMRI) has demonstrated altered WM development in preterm infants without focal lesions,[26] which is related to neurodevelopmental performance in early childhood[27] and adolescence. Using dMRI to assess macrostructural connectivity,[28] 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.[29] 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.[30]

Compared with term-born infants, preterm infants at term-corrected age have impaired cortical development with decreased cortical folding[24]; reduced GM volumes are associated with fetal growth restriction and slower postnatal growth.[31]

Factors associated with the preterm birth signature have been elegantly reviewed by Boardman and Counsell. 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.[20]

NEURODEVELOPMENTAL OUTCOMES OF PRETERM INFANTS

Although rates of severe neurological disability, cerebral palsy (CP) and intellectual disability are reduced compared with 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.[9 32]

While 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.[33 34] 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.[33 34] 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.[35]

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.[36] 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)

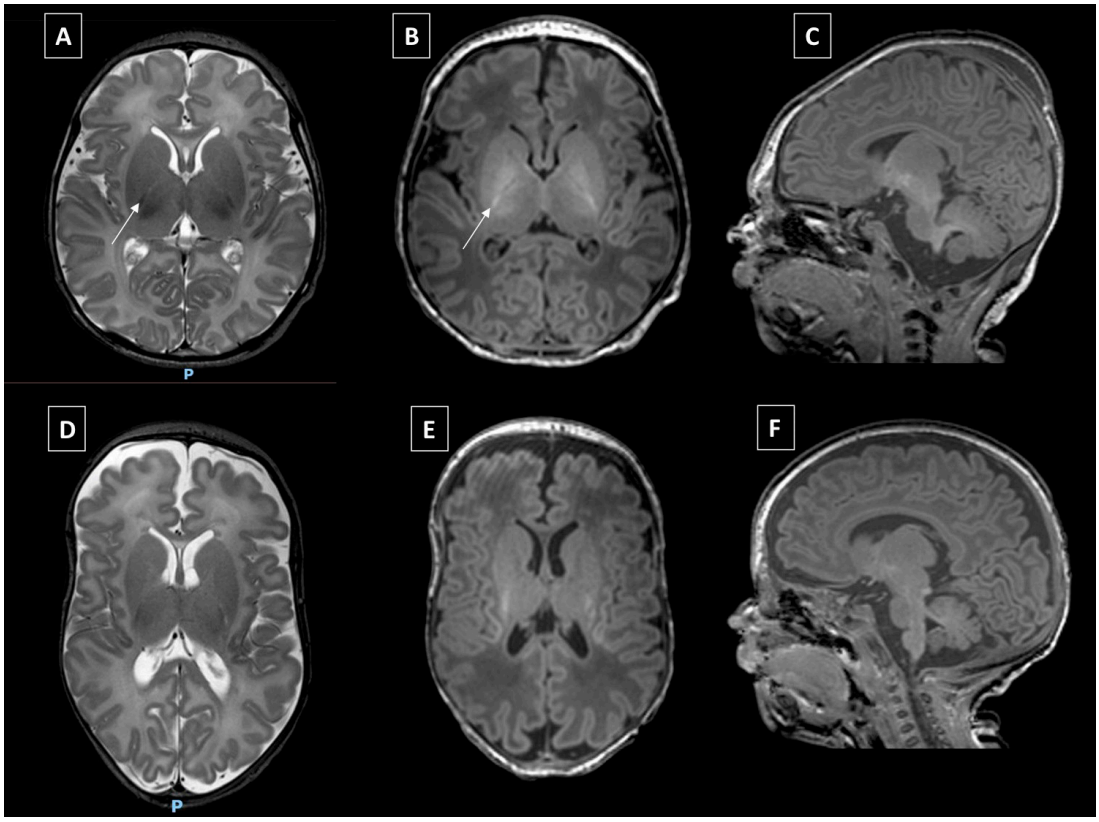

Figure 4 MRI images—term and preterm infant. Representative MRI findings of a term-born and a preterm infant imaged at term-corrected age. Top row: 3T images from a term-born infant born at 41 weeks+4 days and scanned at a postmenstrual age of 42 weeks+1 day. Axial T2 weighted (A), T1 weighted (B) and sagittal T1 (C) weighted images shown. Note the subgaleal collection in the superior parietal convexity. The low T2 and high T1 signal from myelin in the posterior limb of the internal capsule is shown by arrows in A and B. Note also the symmetrical small ventricles and small extracerebral and interhemispheric space in the term-born baby. Lower row (D–F): 3T images from a baby born at 32+3 days and scanned at 40 weeks 5 days. Axial T2 weighted (D), T1 weighted (E) and sagittal (F). Note the scaphocephalic skull shape typical of preterm infants, mildly dilated ventricles, subependymal pseudocysts, probably secondary to a preceding GMH. The myelination is appropriate for age and the basal ganglia structures are unremarkable. In other planes (not seen in these images), punctate white matter lesions are seen. GMH, germinal matrix haemorrhage.

moderate impairment at 3 years.[32] 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[35] (figure 5).

Outcomes at school age or beyond are more valid compared with earlier assessments.[33] Male gender and lower maternal education are associated with both lower early learning composite scores and a decline in scores over time.[34] Bronchopulmonary dysplasia is found to be a crucial factor for cognitive outcome.

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.[33]

Prematurity is the most frequent cause of CP, with an incidence of 9.1% in adults born at 23–27 weeks' gestation inclusive. The spastic subtype accounts for 96% of CP in preterm infants, with 60% being spastic diplegia and 17% spastic quadriplegia.[37]

Motor difficulties associated with DCD, although often considered 'minor', can have a significant impact on the child's abilities.[33]

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.[37]

Cognitive scores at school age and beyond are 11–12 points lower in children born preterm, with mean IQ being 5–7 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 visual–motor integration are particular challenges in preterm survivors.[33]

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 (eg, oral, auditory, tactile, visual).[33]

Extremely preterm infants are four times at risk of attention deficit hyperactivity disorder as compared with term infants with a fourfold increase in risk of autistic spectrum disorder.[38] Psychiatric disorders occur in approximately 25% of those born preterm.[33 37]

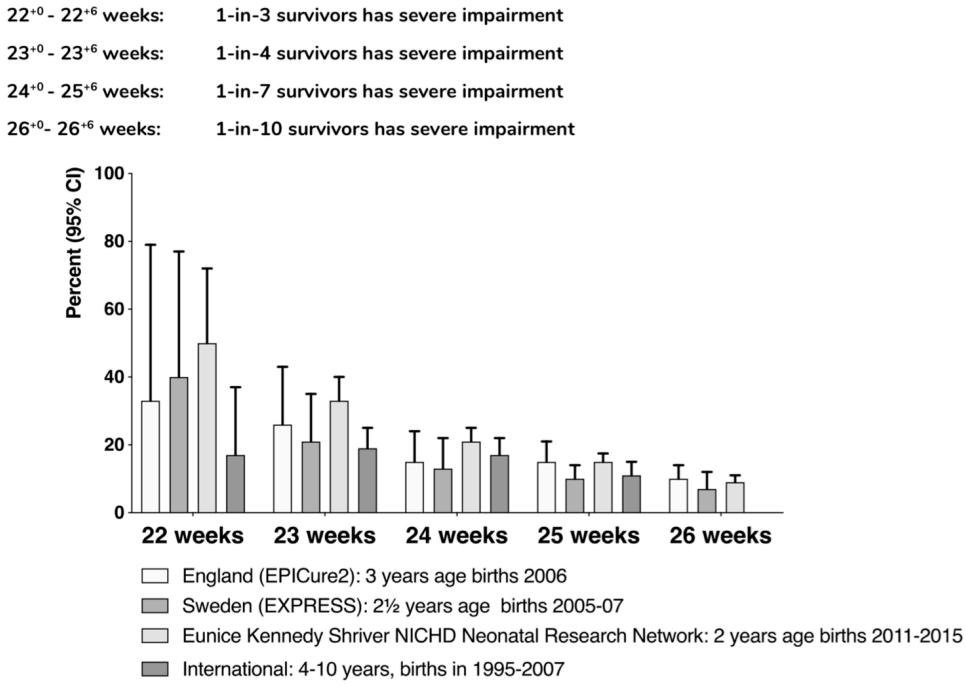

Figure 5 Prevalence of severe neurodevelopmental impairment in England (2006) compared with reported rates from recent international publications. Source: Mactier *et al*, BAPM 2019. NICHD, National Institute of Child Health and Human Development.

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 phonological memory are seen at an older age.[33]

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.[33 37]

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 sulfate is recommended for fetal neuroprotection. Attention to detail with appropriate expertise and facilities at delivery and in everyday management are essential for healthy brain development. Caffeine, used for apnoea of prematurity, is neuroprotective in preclinical models[39] and improves survival without neurodevelopmental disability.[40] 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.[41]

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,[42] 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.[43] Stem cell or exosomal therapies are particularly promising for protection, regeneration and repair of the injured developing brain. Mesenchymal stem cells (MSCs) are attractive because of their low immunogenicity, self-renewing capacity, multilineage 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.[44 45] Administration of MSC is possible intranasally, with stem cells migrating or 'homing' to the injured regions within 2 hours[46]; this opens up great possibilities for treatment of preterm babies over the course of their stay in the 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.[47] However, further clinical research is needed; on recent systematic review of clinical studies, there is no evidence of benefit of stem cell-based or exosome-based therapies for treatment of GMH-IVH, or any other brain injury in the preterm infant.[48]

Non-medical therapies

Admission to the 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.[49] Animal data suggest that prolonged physical separation between parent and newborn alters brain development and results in higher cortisol levels in the infants[50–52] and is associated with stress and anxiety in parents.[53]

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 NICUs. These interventions are designed to allow optimal neurobehavioural development of the infant. A

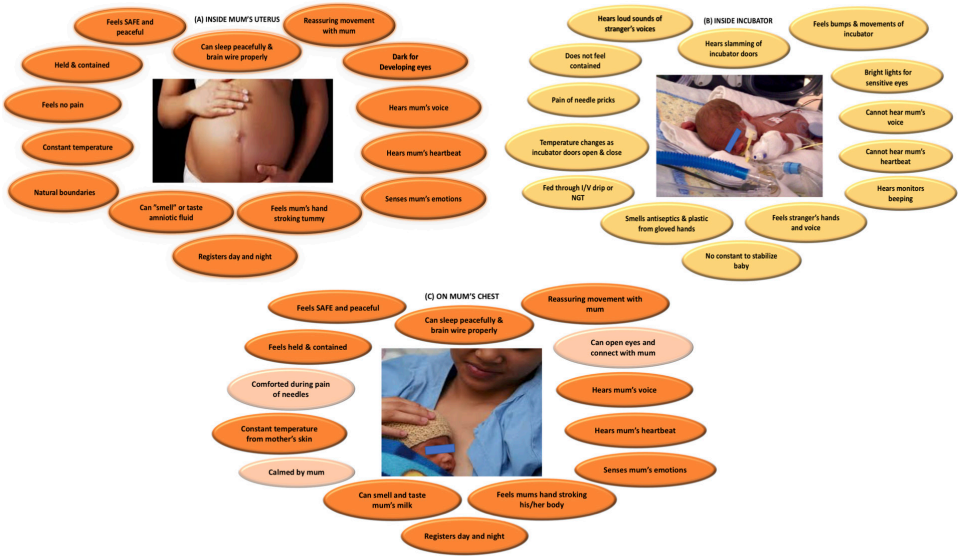

Figure 6 The preterm infant's neurosensory experience in three different environments: (A) inside mum's uterus—feels safe, peaceful and reassured by mum; (B) inside incubator—undergoes several uncomfortable, painful and non-reassuring stimuli; (C) on mum's chest during skin to skin—most sensations simulate the in-utero experience and the infant feels safe, peaceful and reassured by mum. Adapted from Jill Bergman. I/V, intravenous; NGT, nasogastric tube.

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 and 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.[54]

Improved long-term outcomes in infant cognitive, motor and emotional functioning due to NIDCAP in the NICU have been reported up to school age. Enhanced parent confidence and competence is also well documented.[54] Meta-analysis of studies thus far has, however, failed to show significant benefits, likely due to lack of good quality large trials.[55]

Skin-to-skin contact (SSC) and kangaroo mother care (KMC) (figure 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 neurobehavioural development, improving breast feeding, reducing neonatal morbidities, parental anxiety, neonatal stress scores, nosocomial infections, hypothermia and length of stay.[56 57] Earlier and longer contact provides greater benefit and studies have alluded to a dose–response relationship.[58]

SSC and KMC have been shown to confer several benefits to the preterm brain with increased brain maturation,[59] improved connectivity,[60] improved cerebral blood flow,[61] and a positive influence on brain networks and synaptic efficacy up to adolescence.[62] KMC is also shown to increase oxytocin levels and decrease cortisol reactivity in term infants.[63] Studies allude to a lasting impact on self-regulation skills later in infancy,[64] improved executive functioning at 5 and 10 years of life,[65] and significant, long-lasting social and behavioural protective effects even after 20 years of the intervention.[66] Further longer term effect studies of KMC on cognitive and motor development, socioemotional skills and temperament are needed.[64]

Exposure to neonatal pain has been linked to impaired brain development in preterm infants,[67] neonatal pain experience in animals may lead to physical damage or even death of young neurons in the brain.[68] 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 biobehavioural outcomes. KMC accelerates neurophysiological maturation of premature neonates[59] 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.[56]

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

Breast feeding is 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.[69] The positive impact of breast feeding on intellectual development has subsequently been established with evidence of a lasting impact through to adulthood.[70] Improvement in cognitive development is even greater in preterm and very low birthweight infants.[71]

Adolescents that were breast fed in infancy have an increase in total WM, subcortical GM and parietal lobe cortical thickness. Studies using evoked potentials suggest delayed or immature myelination of early neural pathways in formula-fed infants as compared with 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 WM tracts and cerebral structural connectivity. These effects had a dose-dependent relationship with breast milk exposure.[72 73]

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.[49]

By encouraging parental presence, FCC facilitates parent–infant closeness, including SSC and breast feeding, and synchronises cortisol variation between the preterm infant and mother. Several mechanisms may be 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,[74] and all enhancing neurological, neurobehavioural and neurocognitive outcomes in preterm infants.[53 75] Close physical and emotional contact between parent and preterm infant also reduces short-term and long-term parental stress[76] and decreases infant's cortisol levels and pain responses.[53]

Electroencephalogram 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.[77] Other reported benefits of FCC include reduction in length of stay, and moderate to severe bronchopulmonary dysplasia,[49] which in itself is a strong predictor of poor neurodevelopmental outcome.

Family-integrated care (FIC) is a more recent concept which draws on all the essential elements of FCC 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 multicentre randomised controlled trail, FIC significantly improved infant weight gain and parental stress and anxiety.[78] Improvement in breastfeeding rates and length of stay has also been reported.

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 in 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:S2.
2 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:F208–15.
3 Younge N, Goldstein RF, Bann CM, *et al*. Survival and neurodevelopmental outcomes among Periviable infants. *N Engl J Med* 2017;376:617–28.
4 Cheong JLY, Olsen JE, Huang L, *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:e037507.
5 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;105:232–9.
6 Silbereis JC, Pochareddy S, Zhu Y, *et al*. The cellular and molecular landscapes of the developing human central nervous system. *Neuron* 2016;89:248–68.
7 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;194:101883.
8 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;59:350–71.
9 Schneider J, Miller SP. Preterm brain injury: white matter injury. *Handb Clin Neurol* 2019;162:155–72.
10 Pletikos M, Sousa AMM, Sedmak G, *et al*. Temporal specification and bilaterality of human neocortical topographic gene expression. *Neuron* 2014;81:321–32.
11 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:e265.
12 Stoll BJ, Hansen NI, Adams-Chapman I, *et al*. Neurodevelopmental and growth impairment among extremely low-birth-weight infants with neonatal infection. *JAMA* 2004;292:2357–65.
13 Vasung L, Abaci Turk E, Ferradal SL, *et al*. Exploring early human brain development with structural and physiological neuroimaging. *Neuroimage* 2019;187:226–54.
14 Lickliter R. The integrated development of sensory organization. *Clin Perinatol* 2011;38:591–603.
15 McGowan EC, Vohr BR. Impact of nonmedical factors on neurobehavior and language outcomes of preterm infants. *Neoreviews* 2019;20:e372–84.
16 Cheong JLY, Burnett AC, Treyvaud K, *et al*. Early environment and long-term outcomes of preterm infants. *J Neural Transm* 2020;127:1–8.
17 Groenendaal F, Termote JUM, van der Heide-Jalving M, *et al*. Complications affecting preterm neonates from 1991 to 2006: what have we gained? *Acta Paediatr* 2010;99:354–8.
18 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;7:13250.
19 Volpe JJ. The encephalopathy of prematurity--brain injury and impaired brain development inextricably intertwined. *Semin Pediatr Neurol* 2009;16:167–78.
20 Boardman JP, Counsell SJ. Invited review: factors associated with atypical brain development in preterm infants: insights from magnetic resonance imaging. *Neuropathol Appl Neurobiol* 2020;46:413–21.
21 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;41:1509–16.
22 Padilla N, Alexandrou G, Blennow M, *et al*. Brain growth gains and losses in extremely preterm infants at term. *Cereb Cortex* 2015;25:1897–905.
23 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;68:145–50.

24 Ball G, Boardman JP, Aljabar P, *et al*. The influence of preterm birth on the developing thalamocortical connectome. *Cortex* 2013;49:1711–21.
25 Nosarti C, Giouroukou E, Healy E, *et al*. Grey and white matter distribution in very preterm adolescents mediates neurodevelopmental outcome. *Brain* 2008;131:205–17.
26 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;35:1021–7.
27 Ball G, Pazderova L, Chew A, *et al*. Thalamocortical connectivity predicts cognition in children born preterm. *Cereb Cortex* 2015;25:4310–8.
28 Brown CJ, Miller SP, Booth BG, *et al*. Structural network analysis of brain development in young preterm neonates. *Neuroimage* 2014;101:667–80.
29 Ball G, Aljabar P, Zebari S, *et al*. Rich-club organization of the newborn human brain. *Proc Natl Acad Sci U S A* 2014;111:7456–61.
30 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.
31 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;5:168ra8.
32 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.
33 Synnes A, Hicks M. Neurodevelopmental outcomes of preterm children at school age and beyond. *Clin Perinatol* 2018;45:393–408.
34 Yaari M, Mankuta D, Harel-Gadassi A, *et al*. Early developmental trajectories of preterm infants. *Res Dev Disabil* 2018;81:12–23.
35 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:F235–F234.
36 Haslam MD, Lisonkova S, Creighton D, *et al*. Severe neurodevelopmental impairment in neonates born preterm: impact of varying definitions in a Canadian cohort. *J Pediatr* 2018;197:75–81.
37 Rogers EE, Hintz SR. Early neurodevelopmental outcomes of extremely preterm infants. *Semin Perinatol* 2016;40:497–509.
38 Limperopoulos C, Bassan H, Sullivan NR, *et al*. Positive screening for autism in ex-preterm infants: prevalence and risk factors. *Pediatrics* 2008;121:758–65.
39 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;57:2194–205.
40 Schmidt B, Roberts RS, Davis P, *et al*. Long-term effects of caffeine therapy for apnea of prematurity. *N Engl J Med* 2007;357:1893–902.
41 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;218:1–18.
42 Rangarajan V, Juul SE. Erythropoietin: emerging role of erythropoietin in neonatal neuroprotection. *Pediatr Neurol* 2014;51:481–8.
43 Juul SE, Comstock BA, Wadhawan R, *et al*. A randomized trial of erythropoietin for neuroprotection in preterm infants. *N Engl J Med* 2020;382:233–43.
44 Ahn SY, Chang YS, Sung DK, *et al*. Mesenchymal stem cells prevent hydrocephalus after severe intraventricular hemorrhage. *Stroke* 2013;44:497–504.
45 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.
46 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.
47 Keller T, Körber F, Oberthuer A, *et al*. Intranasal breast milk for premature infants with severe intraventricular hemorrhage-an observation. *Eur J Pediatr* 2019;178:199–206.
48 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:Cd013201.
49 Yu X, Zhang J. Family-centred care for hospitalized preterm infants: a systematic review and meta-analysis. *Int J Nurs Pract* 2019;25:e12705.
50 Nishi M. Effects of early-life stress on the brain and behaviors: implications of early maternal separation in rodents. *Int J Mol Sci* 2020;21:7212.
51 Chen M, He G, Li Q. Maternal deprivation promotes hippocampal neuronal apoptosis via ERK1/2 signaling. *Front Biosci* 2018;23:1923–32.
52 Feng X, Wang L, Yang S, *et al*. Maternal separation produces lasting changes in cortisol and behavior in rhesus monkeys. *Proc Natl Acad Sci U S A* 2011;108:14312–7.
53 Flacking R, Lehtonen L, Thomson G, *et al*. Closeness and separation in neonatal intensive care. *Acta Paediatr* 2012;101:1032–7.
54 Als H, McAnulty GB. The newborn individualized developmental care and assessment program (NIDCAP) with kangaroo mother care (KMC): comprehensive care for preterm infants. *Curr Womens Health Rev* 2011;7:288–301.
55 Ohlsson A, Jacobs SE. NIDCAP: a systematic review and meta-analyses of randomized controlled trials. *Pediatrics* 2013;131:e881–93.
56 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.
57 Johnston C, Campbell-Yeo M, Disher T, *et al*. Skin-to-skin care for procedural pain in neonates. *Cochrane Database Syst Rev* 2017;2:Cd008435.
58 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:Cd003519.
59 Kaffashi F, Scher MS, Ludington-Hoe SM, *et al*. An analysis of the kangaroo care intervention using neonatal EEG complexity: a preliminary study. *Clin Neurophysiol* 2013;124:238–46.
60 Scher MS, Ludington-Hoe S, Kaffashi F, *et al*. Neurophysiologic assessment of brain maturation after an 8-week trial of skin-to-skin contact on preterm infants. *Clin Neurophysiol* 2009;120:1812–8.
61 Korraa AA, El Nagger AAI, Mohamed RAE-S, *et al*. Impact of kangaroo mother care on cerebral blood flow of preterm infants. *Ital J Pediatr* 2014;40:83.
62 Schneider C, Charpak N, Ruiz-Peláez JG, *et al*. Cerebral motor function in very premature-at-birth adolescents: a brain stimulation exploration of kangaroo mother care effects. *Acta Paediatr* 2012;101:1045–53.
63 Hardin JS, Jones NA, Mize KD, *et al*. Parent-training with kangaroo care impacts infant neurophysiological development & mother-infant neuroendocrine activity. *Infant Behav Dev* 2020;58:101416.
64 Akbari E, Binnoon-Erez N, Rodrigues M, *et al*. Kangaroo mother care and infant biopsychosocial outcomes in the first year: a meta-analysis. *Early Hum Dev* 2018;122:22–31.
65 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;75:56–64.
66 Charpak N, Tessier R, Ruiz JG, *et al*. Twenty-year follow-up of kangaroo mother care versus traditional care. *Pediatrics* 2017;139:e20162063.
67 Brummelte S, Grunau RE, Chau V, *et al*. Procedural pain and brain development in premature newborns. *Ann Neurol* 2012;71:385–96.
68 Dührsen L, Simons SHP, Dzietko M, *et al*. Effects of repetitive exposure to pain and morphine treatment on the neonatal rat brain. *Neonatology* 2013;103:35–43.
69 Newton N. The uniqueness of human milk. psychological differences between breast and bottle feeding. *Am J Clin Nutr* 1971;24:993–1004.
70 Lawrence RA. Supporting Breastfeeding/Early Childhood Social and Emotion Development. In: Tremblay RE, Boivin M, RDeV P, eds. *Encyclopedia on early childhood development [online]*, 2008.
71 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:e0116552.
72 Deoni SCL, Dean DC, Piryatinsky I, *et al*. Breastfeeding and early white matter development: a cross-sectional study. *Neuroimage* 2013;82:77–86.
73 Blesa M, Sullivan G, Anblagan D, *et al*. Early breast milk exposure modifies brain connectivity in preterm infants. *Neuroimage* 2019;184:431–9.
74 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.
75 Rahkonen P, Heinonen K, Pesonen A-K, *et al*. Mother-child interaction is associated with neurocognitive outcome in extremely low gestational age children. *Scand J Psychol* 2014;55:311–8.
76 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;39:375–86.
77 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;104:670–7.
78 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;2:245–54.