A new neurological focus in neonatal intensive care

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Abstract | Advances in the care of high-risk newborn babies have contributed to reduced mortality rates for premature and term births, but the surviving neonates often have increased neurological morbidity. Therapies aimed at reducing the neurological sequelae of birth asphyxia at term have brought hypothermia treatment into the realm of standard care. However, this therapy does not provide complete protection from neurological complications and a need to develop adjunctive therapies for improved neurological outcomes remains. In addition, the care of neurologically impaired neonates, regardless of their gestational age, clearly requires a focused approach to avoid further injury to the brain and to optimize the neurodevelopmental status of the newborn baby at discharge from hospital. This focused approach includes, but is not limited to, monitoring of the patient's brain with amplitude-integrated and continuous video EEG, prevention of infection, developmentally appropriate care, and family support. Provision of dedicated neurocritical care to newborn babies requires a collaborative effort between neonatologists and neurologists, training in neonatal neurology for nurses and future generations of care providers, and the recognition that common neonatal medical problems and intensive care have an effect on the developing brain.

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Introduction

Over the past 40 years tremendous progress has been made in neonatology, especially with regard to providing life-support therapy and care for premature babies. Monitoring of heart rate, blood pressure and oxygen saturation are routine practices in neonatal intensive care. Despite the technological advances in caring for sick neonates, however, rates of neurological compromise remain high.[1,2] As a result, neonatologists are increasingly focusing on brain function and development in newborn babies. Several areas are undergoing active research: investigations into the brain's susceptibility to injury; the influence of neonatal care on brain development and injury; the relationship between brain injuries in neonates and long-term neurological status; and potential therapeutic agents to improve long-term neurological outcomes.[3]

Research into brain development has proved that responses to injury are specific to developmental stages and age.[3,4] The concept that different brain regions show 'selective vulnerability' to injury at different gestational ages has been demonstrated in animal models and is observed in human studies;[3] the white matter of the brain is most vulnerable in preterm babies and gray matter injury is most common in term neonates. These patterns of vulnerability result in specific neurological sequelae, such as spastic diparesis in premature babies and spastic quadriparesis in severely injured babies born at term.

Competing interests
The authors declare no competing interests

Despite the advances in research, few clinical trials have investigated neuroprotective strategies in preterm and term infants; to date, only hypothermia has shown efficacy in decreasing the risk of death or disability in term neonates with hypoxic–ischemic encephalopathy (HIE), although complete protection from this condition has not been realized with hypothermia alone.[5,6] The neurological sequelae of prematurity (such as intraventricular hemorrhage, white matter injury, and periventricular leukomalacia) have not been addressed with any current therapies, although awareness is increasing about the importance of providing optimal critical care that focuses on neuroprotection.

In this Review we highlight the advances in basic science, clinical studies and translational research that have provided a foundation for focused neurological intensive care in newborn babies, and describe a model of shared care, in which neonatologists and neurologists jointly manage sick neonates who are at risk of long-term neurodevelopmental impairment.

Advances in neuroprotective therapy

Therapeutic hypothermia

Therapeutic hypothermia is the first neuroprotective strategy that has demonstrated efficacy for neonatal HIE in multiple randomized controlled trials.[6] These studies involved a total of more than 1,300 infants with HIE; a meta-analysis that included 767 of these neonates concluded that therapeutic hypothermia significantly reduced the risk of death or disability at 18 months (relative risk 0.81, 95% CI 0.71–0.93 versus standard

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Key points

- Clinical trials in brain development and the pathophysiology of brain injury in premature and term neonates promote the development of new therapies for neurological conditions in neonates
- Amplitude-integrated EEG and near-infrared spectroscopy enable monitoring of brain function during critical illness and improved ability to detect and treat neonatal seizures, and might provide early prognostic information
- Hypothermia therapy is the only approach proven to decrease morbidity and mortality from neonatal hypoxic–ischemic encephalopathy in term infants; this treatment is being implemented in hospitals around the world
- In the neonatal neurocritical care model, neonatologists and neurologists work together to care for newborn babies with primary and secondary neurological conditions

care), and the number of neonates needed to be treated for one newborn baby to be free of death or disability was nine (95% CI 5–25)[6]—an impressively low number considering the high cost of lifelong disability.

Currently, hypothermia is not the standard of care in all institutions, but the 2010 International Liaison Committee on Resuscitation guidelines state that infants born at (or near) term with moderate to severe HIE should be offered therapeutic hypothermia, to be initiated and conducted under clearly defined protocols at neonatal intensive care facilities that provide multidisciplinary care and follow-up.[7] Although simple in concept, provision of such therapy requires clinical expertise in evaluating the neonate's neurological status, nursing expertise in applying the therapy and monitoring for complications, as well as the availability of monitoring for seizures, imaging studies after completion of therapy, and long-term developmental follow-up. Careful attention must be paid to the clinical management of newborn babies with HIE, regardless of whether hypothermia is implemented, as hypoxic–ischemic insults are not limited to the brain. Such insults might result in systemic complications, such as hypoglycemia, and affect other vital organs (heart, lungs, kidneys, liver, bone marrow), the dysfunction of which may contribute to further brain injury.[8,9] Unfortunately, no single therapy adequately ameliorates all forms of brain injury in newborn babies. The evidence from trials indicates that hypothermia is not 100% efficacious[6] and the search for potential new adjuvant therapies must continue.

Erythropoietin

An exciting therapeutic approach being tested in pilot clinical trials in hypoxic–ischemic encephalopathy is erythropoietin. Preclinical data from rodent models of neonatal HIE have demonstrated both short-term and long-term histological and behavioral improvement after treatment with this agent.[10] Single-dose and multiple-dose treatment regimens of erythropoietin, following neonatal focal ischemic stroke in rats, reduced cerebral infarct volume and improved both short-term sensorimotor[11] and long-term cognitive[12] outcomes, but the neuroprotective benefits seemed to last longer in female than male rats.[13] In a rodent model of neonatal HIE, erythropoietin treatment initiated 24 h after induction of hypoxic ischemia also decreased brain injury.[14] In addition, erythropoietin can enhance neurogenesis[12] and direct multipotent neural stem cells toward a neuronal cell fate.[15]

In humans, erythropoietin is a safe and effective treatment for anemia in premature babies.[16] Neonates with extremely low birthweight have tolerated erythropoietin doses of 500–2,500 U/kg,[17] and safety studies are ongoing. However, erythropoietin is given in much higher doses for neuroprotection (1,000–5,000 U/kg) than for anemia, in the hope that an effective level of erythropoietin will cross the blood–brain barrier, although the exact pharmacokinetics of erythropoietin transport into the brain in humans are unknown. For human neonates with HIE, early studies have demonstrated the safety and benefit of erythropoietin treatment, with treated neonates showing improved neurological outcomes at 18 months of age;[18,19] however, large randomized trials have yet to be performed. The current evidence is insufficient to recommend adjunctive erythropoietin therapy for newborn babies with HIE who are undergoing hypothermia, but a multicenter trial to investigate the safety and pharmacokinetics of this approach is currently being performed.

Xenon in combination with hypothermia

The best combination therapy for neonatal HIE should provide long-lasting neuroprotection while also enhancing repair and regeneration of the brain. One promising adjuvant treatment is xenon. This noble gas is an *N*-methyl-D-aspartate (NMDA) antagonist approved for use as a general anesthetic in Europe, and has also shown promise as a neuroprotective agent.[20] Xenon is superior to other NMDA antagonists as a potent blocker of excitotoxic damage and acts through inhibition of α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) and kainate receptors, reduction of glutamate release, and potential effects on ion channels.[21–23] In animal models, a combination of xenon and hypothermia treatment (initiated 4 h after induction of neonatal hypoxic ischemia) provided synergistic histological and functional protection, which was evident up to 30 days after injury.[24] An additive effect of xenon was shown in 7-day-old rats with hypoxic ischemia that were cooled to 32 °C and then received 50% xenon in air; the improvement in histology scores and long-term functional performance after this combination treatment exceeded the benefits of either therapy in isolation.[25] Data from a piglet model of global hypoxic–ischemic insult show that neonates that received combined xenon and hypothermia treatment had reduced cerebral lactate accumulation.[20] Pilot studies are underway to assess the safety of xenon treatment in human neonates.[26]

Antioxidants

N-acetylcysteine, a scavenger of oxygen radicals that can restore intracellular glutathione levels, is approved for use in neonates. In neonatal rats with HIE treated with systemic hypothermia, the addition of *N*-acetylcysteine reduced brain volume loss at both 2 weeks and 4 weeks

after the hypoxic ischemic insult.[27] No randomized trials of *N*-acetylcysteine in human neonates with HIE have been performed.

Another antioxidant, melatonin, has neuroprotective properties in small and large animal models.[28–31] In addition, melatonin promotes oligodendroglial maturation in injured white matter in neonatal rats.[32] Studies are underway to assess the combined benefits of hypothermia with melatonin.[33]

Monitoring and supportive care

HIE is not the only form of brain injury in term neonates: stroke occurs in one in 1,600–5,000 term newborn babies.[34] Although no therapies currently exist for neonatal stroke, infants with this condition would benefit from dedicated neurological intensive care as they most commonly present with seizures, which can be difficult to control. In addition, advanced imaging techniques might identify the presence of a clot in either the venous or arterial system, which could be treated to prevent extension of the infarct.[35] Preterm neonates can also sustain brain injuries, including intraventricular hemorrhage, which, when severe, may cause progressive dilatation of the ventricles and result in injury of the brain parenchyma. The management of ventricular dilatation remains under investigation, but will require close monitoring of the brain with ultrasonography and good communication between neonatologists, neurologists and neurosurgeons.[36,37]

Anticonvulsants

The evidence increasingly suggests that seizures contribute to brain injury in term newborn babies.[38] The use of hypothermia in combination with anticonvulsants is appealing, as these drugs are already being used in neonatal intensive care units to treat seizures in term neonates.

Here, we highlight currently available antiepileptic medications that might have secondary neuroprotective properties. At present, the evidence is insufficient to recommend one anticonvulsant drug over another with regard to achieving secondary neuroprotection. Each neonatal intensive care unit should use the drugs with which they are familiar and develop protocols for their use in seizure therapy with the goal of achieving rapid seizure cessation.

Phenobarbital

Phenobarbital is the medication most commonly used to treat neonatal seizures,[36] even though it is known to induce neuronal apoptosis in the developing rodent brain[37] and treatment with this agent does not achieve seizure-cessation in all patients.[39–41] In a rodent model of HIE, the addition of adjunctive phenobarbital treatment to delayed-onset hypothermia resulted in improved short-term and long-term neurological outcomes, and in reduced neuronal pathology as assessed via histology.[42] However, data from retrospective cohort studies that assessed the prophylactic use of phenobarbital in neonates with HIE did not demonstrate significant reductions in death or neurodevelopmental impairment among treated infants.[43,44] Randomized clinical trials of hypothermia plus phenobarbital have not yet been performed in human neonates.

Topiramate

Topiramate is an effective, clinically available anticonvulsant that has shown some synergistic effects in combination with hypothermia in animal models, but only if used immediately after the induction of hypoxic ischemia.[45] The anticonvulsant effects of topiramate seem to be mediated through multiple mechanisms, such as inhibition of carbonic anhydrase isozymes, modulation of AMPA and kainate receptors, as well as γ-aminobutyric acid type A receptor-activated ion channels, and voltage-activated Na^+ and Ca^{2+} channels.[46] Topiramate increased the efficacy of a suboptimal delayed hypothermia treatment (that is, administered 3 h after the hypoxic–ischemic insult) in a rat model of neonatal stroke.[45] In this study, neither topiramate nor delayed hypothermia alone conferred a neuroprotective effect, but rats that received topiramate plus delayed hypothermia had both improved functional performance and a reduction in the severity of brain injury after 3 weeks of recovery.[45]

Before combination treatment with topiramate (or any other agent) plus hypothermia can be considered for clinical trials, understanding how hypothermia affects the pharmacokinetics of each drug is essential. In a study of 13 asphyxiated neonates who were being treated with therapeutic whole-body hypothermia, daily oral administration of topiramate at a dose of 5 mg/kg during hypothermia led to plasma concentrations of this drug within the reference range of 5–20 mg/l,[47] showing that absorption of orally administered topiramate was maintained during hypothermia. No apparent effect on topiramate concentrations was detected in three neonates who also received phenobarbital.[44]

Levetiracetam

Levetiracetam, a regulator of excitatory synaptic transmission mediated by AMPA and NMDA receptors, has attracted interest as a treatment for refractory neonatal seizures, owing to its good bioavailability and the availability of intravenous formulations.[48] Interestingly, in contrast to several traditional anticonvulsant drugs, such as phenobarbital and phenytoin, levetiracetam does not cause apoptosis in the developing brain, even when used at doses several times higher than those needed to obtain a therapeutic effect, although it can worsen the toxic effects of phenytoin.[49] Levetiracetam might be an especially good candidate for the treatment of seizures in neonates, but its use and safety in asphyxiated newborn babies must be studied carefully.

Advances in brain monitoring

EEG techniques

The ability to monitor electrical activity in the brain and to detect seizures has evolved from paper traces to digital recordings with video. The advent of digital video-EEG recordings enables the collection of large amounts of data and the capture of live recordings that can be reviewed

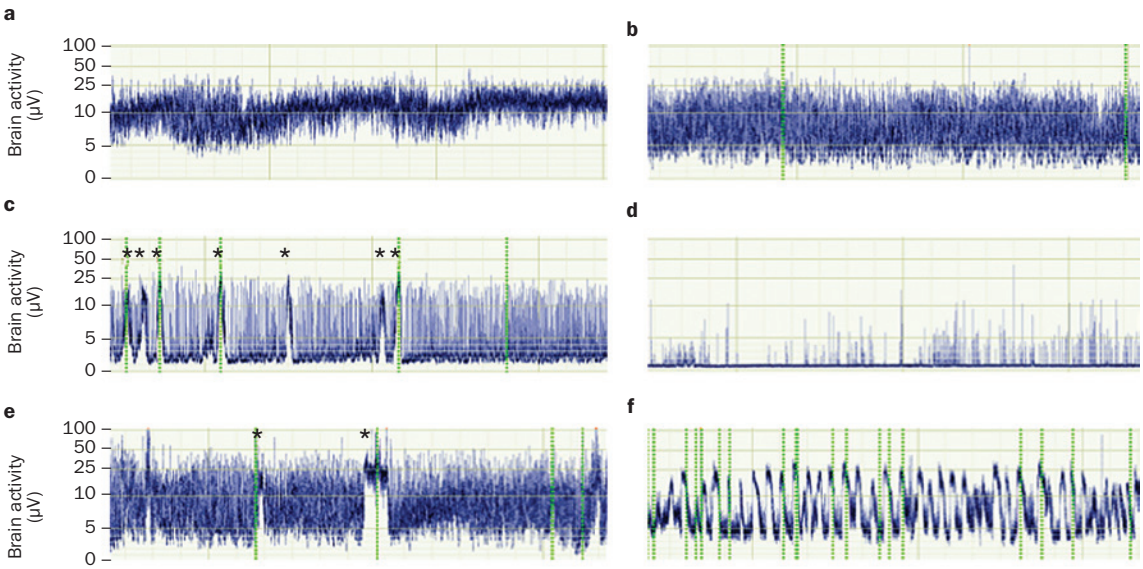

Figure 1 | Patterns of electrocortical background activity observed using aEEG. The patterns are classified as follows: **a** | continuous normal voltage (normal background pattern for term infants characterized by continuous activity with lower amplitude at [5]–7–10 μV and maximum amplitudes at 10–25–[50] μV). **b** | Discontinuous normal voltage (mildly abnormal in term infants, can be normal in some preterm infants depending on the postmenstrual age at the time of monitoring; characterized by discontinuous activity with some variability in the minimum amplitude, but mainly <5 μV and maximum amplitude >10 μV). **c** | Burst suppression (abnormal background pattern characterized by minimum amplitude without variability at 0–2 μV intermixed with bursts of high-voltage activity >25 μV) with seven short seizures (asterisks). **d** | Isoelectric or flat trace (severely abnormal background pattern with inactive background corresponding with electrocerebral inactivity. **e** |Two seizures (asterisks) can be identified by a rise in the upper and lower margins against a discontinuous normal voltage background. **f** | Saw-tooth pattern of status epilepticus.

remotely. EEG is the gold-standard technique for seizure detection; however, the use of EEG requires specialized technicians for the application of leads and a physician trained in EEG interpretation. Additional training is required to interpret neonatal EEG recordings, to recognize the developmental changes and maturity status of the brain in newborn babies. Recorded brain activity in neonates is classified into various background patterns; the presence or absence of specific features in these patterns assists in the assessment of brain development and in the identification of neonates with possible brain injury.

Compared with standard EEG, amplitude-integrated EEG (aEEG) is a newer bedside monitoring technique, which was initially developed to monitor the depth of anesthesia during surgery, and brain activity after cardiac arrest in adults. [50] The technique was subsequently adapted for use in asphyxiated neonates.[50,51] The monitors used to capture and display aEEG outputs are compact enough to be used at the bedside, and their use in the neurological neonatal intensive care unit requires minimal training. These monitors provide a compressed trace of brain activity that is categorized into background patterns[52] similar to those produced by conventional EEG, which enable the identification of sleep–wake patterns and seizures (Figure 1).

EEG patterns as a predictor of outcome

Multiple studies have investigated the relationship between the EEG or aEEG background pattern demonstrated by an infant and their short-term and long-term outcomes. In a review of case histories of neonates with HIE who were not treated with hypothermia, the pattern of background activity observed on EEG at 1 week of life correlated with long-term neurodevelopmental outcomes.[53] In another study, brain activity recorded by EEG within the first 3 days of life correlated with both imaging findings and outcome after 1 week.[54] The first study to investigate the association between early background brain activity (that is, recorded by aEEG within the first 6 h after birth) and neurodevelopmental outcomes at 12–18 months was published in 1995.[51] In this study, aEEG demonstrated good sensitivity, specificity and positive predictive value for neurological outcome.[55] Further studies have shown that the pattern of background activity on aEEG, measured as early as 3 h after birth, is predictive of outcome.[56] In addition, recovery within 24 h from a severely abnormal background and sleep–wake cycling pattern detected on aEEG is predictive of a favorable neurological outcome in neonates with HIE who were not treated with hypothermia.[57,58]

The aEEG activity pattern remains an important predictor of outcome in neonates undergoing therapeutic hypothermia, but the time at which the aEEG activity pattern offers prognostic information is somewhat delayed compared with that in infants who are not undergoing this treatment. [59] Hypothermia-treated neonates who recover their aEEG background activity at up to 48 h after birth can still have a normal outcome.[59]

Similar findings were shown in studies that used continuous video-EEG to monitor infants' brain activity throughout the 72 h of hypothermia treatment for HIE; the background brain activity patterns observed in these neonates during therapy correlated with the severity of brain injury on early MRI (<1 week of life).[56] Continuous video-EEG also revealed that seizures were often clinically silent—of 14 infants with electrographic seizures, eight showed no clinical signs.[60] In this study, normal to mildly abnormal background activity, or patterns that showed a substantial improvement during the first 36 h of hypothermia therapy, correlated with minimal brain injury on post-treatment MRI. The delay in the time at which aEEG (or video EEG) brain activity patterns offer prognostic information in hypothermia-treated neonates is in keeping with the delay in recovery from encephalopathy seen in cooled babies.[61] Increases in regional brain oxygen saturation at 24 h, as measured by near-infrared spectroscopy, have also been associated with unfavorable long-term outcomes in infants with HIE.[62] As decisions must often be made regarding the direction of care in neonates with HIE, additional early predictors of outcome are clearly needed.

Monitoring for seizures

Neonatal seizures are difficult to diagnose accurately, owing to electroclinical dissociation (electrographic seizures that do not display a clinical manifestation), and abnormal movements in sick babies that can be misinterpreted and treated as a seizure.[63] Monitoring with EEG or aEEG is the only method that can accurately identify seizures and monitor the response to anticonvulsant medication. With the advent of aEEG and automated mechanisms of seizure detection, the utility of diagnosis and treatment of seizures is an area of active research. A long-standing debate concerns the effect of seizures on brain injury and long-term outcome, as well as the potentially harmful versus beneficial effects of anticonvulsants on the developing brain.[64] The evidence increasingly suggests that seizures are independently associated with brain injury, alter neuronal connections and brain development, and increase the risk of cerebral palsy and global developmental delay.[38,65–68] In a piglet model of HIE, animals with subclinical or clinical seizures demonstrated statistically significant alterations in metabolite ratios, as determined by proton magnetic resonance spectroscopy.[69] Increased injury was seen in brain tissue samples from piglets that had undergone seizures, and these animals also showed worse abnormalities on neurobehavioral testing than did seizure-free animals.[69] In humans, the results of imaging and long-term follow-up studies of neonates with perinatal asphyxia mirror those of animal studies; newborn human babies with a high clinical seizure burden have substantial derangements in regional brain metabolites, including increased lactate levels (a marker of neuronal injury),[38] and worse motor and cognitive outcomes than babies without seizures.[70] Given these findings, the ability to monitor neonates at risk of seizures with aEEG and/or video-EEG is important.[8]

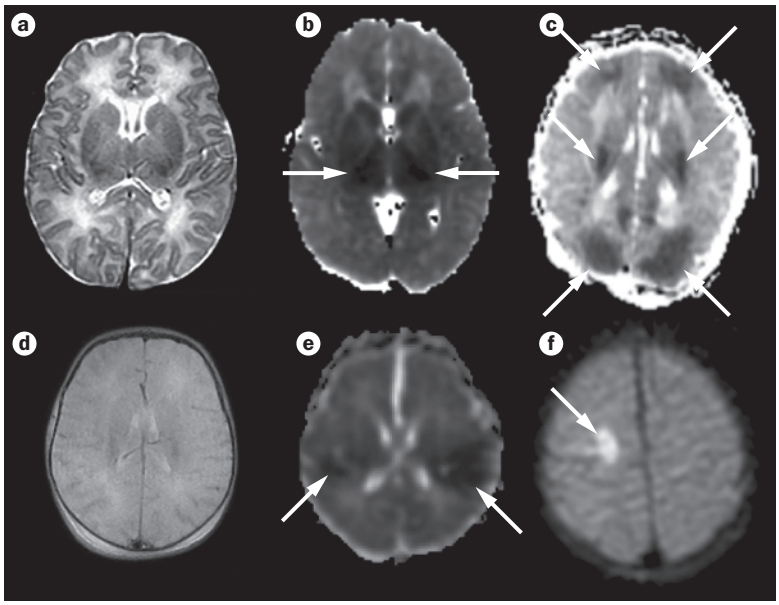

Figure 2 | MRI scans showing normal findings and examples of brain injuries in term newborn babies. **a** | T2-weighted image depicting normal term brain. **b** | Diffusion-weighted MRI scan showing hypoxic–ischemic injury to the deep gray nuclei (arrows). **c** | Diffusion-weighted MRI scan with watershed pattern of hypoxic–ischemic injury (top and bottom arrows point to anterior and posterior watershed regions of the cortex and white matter, central arrows show injury to white matter). **d** | T1-weighted imaged depicting diffuse brain injury secondary to global hypoxic–ischemic insult. **e** | Diffusion-weighted image showing injury to the white matter and cortex (arrows) in an 11-day-old term infant with congenital heart disease. **f** | Diffusion-weighted MRI scan showing focal stroke (arrow) in a term infant who presented with focal seizures on the second day of life.

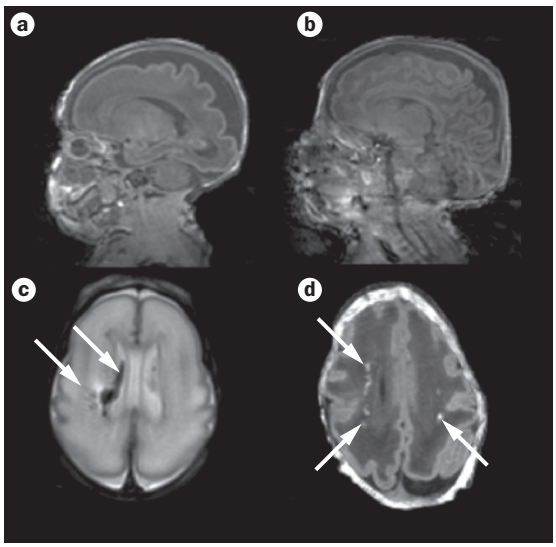

Figure 3 | MRI scans of the brain in preterm newborn babies. **a** | MRI brain scan of a preterm newborn infant imaged at 26–27 weeks' postmenstrual age. **b** | MRI scan of the same infant taken 6 weeks after the scan in panel a. Note the substantial growth and increased complexity of the developing brain. **c** | MRI brain scan of a preterm infant imaged at 29 weeks' postmenstrual age, 1 week after birth showing hemorrhage in the brain tissue and ventricles (arrows). **d** | MRI brain scan of a preterm infant imaged at 30 weeks' postmenstrual age, 2 weeks after birth showing foci of white matter injury (arrows).

Box 1 | Classification of neurological conditions co-managed at the UCSF NICN

At our center, the NICN neurology team is involved in the co-management of all infants with primary or secondary neurological problems. The neurology team conducts daily rounds with the neonatal team, and is available for acute neurological management 24 h a day. Treatment options for patients with acute or emergency conditions are discussed before or at the time of admission to the NICN, whereas those for babies with subacute conditions are discussed during daytime rounds.

Patients with acute or potentially emergency conditions

- Neonatal encephalopathy (caused, for example, by asphyxia, metabolic disorders or infection)
- Known or suspected seizures
- Known or suspected stroke
- Meningitis or encephalitis

Patients with subacute conditions

- Premature newborn babies with ultrasound findings of grade III–IV intraventricular hemorrhage or ventriculomegaly
- Premature newborn babies undergoing routine monitoring with amplitude-integrated EEG (for example, during the first 24–72 h of life in babies of <28 weeks' gestation)
- Patients with a CNS malformation
- Patients with critical illness being monitored with amplitude-integrated EEG

Abbreviations: NICN, neonatal neurological intensive care nursery; UCSF, University of California, San Francisco.

Box 2 | Management of newborn babies with seizures

The management of neonatal seizures varies across centers.[39] No evidence-based guidelines are available regarding the sequence of medications used to achieve seizure cessation.[64] In our NICN, to facilitate management of neonates with seizures EEG is streamed live from the bedside to the EEG reading room and can be reviewed remotely. Communication between all team members is vital to provide appropriate and timely therapy. Anticonvulsant drugs are ordered instantly so that nurses can promptly administer treatment.

- Neurologists are notified about all newborns with possible seizures
- NICN guidelines are followed to manage clinical seizures during transport (lorazepam 0.1 mg/kg or phenobarbital 20 mg/kg initial loading dose)
- The patient is evaluated by the neonatal and neurology teams and assigned to a nurse with training in NICN procedures
- Monitoring with aEEG and video-EEG are initiated (aEEG leads are placed by nursing staff who mark events and notify physicians regarding possible seizures or changes in the background)
- The aEEG output is reviewed after the first 20 min of recording; video EEG output is reviewed after 1 h of recording or when suspicious clinical or aEEG events are identified and at least twice in every 24 h, or more often as clinically indicated
- If electrographic seizures are identified, the following treatment protocol is initiated: phenobarbital ≤40 mg/kg loading dose; fosphenytoin ≤30 mg/kg loading dose; levetiracetam 40 mg/kg loading dose
- 30 min after administration of anticonvulsant medication, the aEEG and video EEG outputs are reviewed, and a plan for further review and communication between the teams is made
- Identification of status epilepticus is considered and managed as an emergency with the goal of timely administration of anticonvulsant medication and seizure cessation
- Video-EEG is continued until the patient is seizure-free for 24 h

Abbreviations: aEEG, amplitude-integrated EEG; NICN, neonatal neurological intensive care nursery.

Imaging in neonatal neurocritical care units

Cranial ultrasonography is the most common form of brain imaging in the neonatal intensive care unit, as it is noninvasive, can be easily performed at the bedside, and is thought to be safe. This technique is most commonly used in premature neonates to screen for intraventricular hemorrhage and to monitor the evolution of white matter lesions and ventricular dilatation. In term newborn babies, cranial ultrasonography can be limited by physical differences between the head of a term neonate and that of a preterm baby, and by the typical location of hypoxic–ischemic injury, such as in the deep gray nuclei and the cortical neurons located in the cerebral convexities —areas that can be difficult to access.[71,72] Ultrasonography can also be limited in its capacity to detect abnormalities of cortical development and problems in the posterior fossa, and it does not provide information on white matter development or maturation, or depict characteristic changes that have been observed in the white matter of neonates with certain metabolic disorders.[71]

In an analysis of data from the Encephalopathy Registry of the Vermont Oxford Network, VT, USA, up to 28% of full-term newborn babies had undergone CT scans; however, this technique is of limited value in neonates and exposes them unnecessarily to high doses of radiation[72] (T. Inder, personal communication). MRI does not employ ionizing radiation, and is safe and useful in both preterm and term infants.[73] Advances in MRI techniques over the past two decades have led to reduced image acquisition times and improvements in the quality of images of the newborn brain. Commercially available MRI-compatible incubators, ventilators and monitors enable physicians to transport sick neonates to the MRI suite safely.[74,75]

MRI in preterm neonates has provided important insights into brain development during periods of critical illness.[76] Advanced MRI techniques also facilitate the study of various aspects of neonatal brain development and function: the way that important communicating fiber tracks develop in premature babies; alterations in brain metabolism at different regions; the effects of prematurity and critical illness on the developing brain; the growth and development of specific brain regions; and the association of these brain regions with various developmental outcomes.[71–75] Imaging studies in high-risk neonates have identified risk factors for acquired brain injury (such as infection and chronic lung disease),[77–80] and provided evidence that specific management or medication strategies (such as caffeine therapy for apnea of prematurity) could have beneficial effects on brain microstructural development.[81,82]

MRI can be used to assess structural changes in the brain in neonates with various forms of hypoxic–ischemic injury (Figure 2). Brain MRI findings in premature infants also demonstrate the rapid growth and gain in complexity of this organ, and can be used to identify common forms of brain injury in such infants (Figure 3). In addition, MRI is increasingly being used to identify imaging features that can act as potential biomarkers, or surrogate measures, of long-term outcome.[83,84] The need

for such measures in neonatal neurology is growing. New therapeutic trials aimed at improving outcomes in school-age children are expensive to fund, as they would require 5–8 years of follow-up. In addition, MRI findings might be used to select patients who are suitable for enrollment in future trials of therapies for neonatal stroke.

Lessons from adult neurocritical care

Neurocritical care is a relatively new subspecialty. In 2002, the Neurocritical Care Society was established with the aim of improving outcomes for patients with life-threatening neurological illnesses, and in 2007 the Accreditation Council for Graduate Medical Education administered the first certification examination in adult neurocritical care. The subspecialty of neurocritical care was initially developed to address the postoperative needs of neurosurgical patients, and has since grown to encompass a broad range of serious neurological conditions, including stroke, status epilepticus, CNS infection, and traumatic brain injury.

Although the developing brain differs enormously from the mature brain, several basic lessons from adult neurocritical care can be applied to the emerging field of neonatal neurocritical care: careful attention to basic physiology (including temperature regulation, glucose homeostasis, oxygenation, and blood pressure support) can improve outcomes by preventing secondary injury in patients with neurological illnesses;[85,86] the use of specialized neurocritical care teams can reduce mortality and improve resource utilization;[87–92] and dedicated units that use a protocol-driven approach can achieve reductions in mortality and increased rates of favorable outcomes.[93–96] Although neurocritical care is a subspecialty that relies heavily on advanced monitoring and imaging techniques, the principles themselves are simple and can be applied at most tertiary care centers.

Shared management

The staffing structure of a neonatal neurocritical care service might vary depending on the needs and capabilities of the institution. Critically ill newborn babies with neurological conditions who are at risk of adverse neurodevelopmental outcomes include children with complex primary medical conditions, such as extreme prematurity, congenital heart disease, multisystem disease, perinatal asphyxia, neonatal seizures, status epilepticus, and acute traumatic brain injury.[97,98] Caring for these children is complex and requires health providers with expertise in both neonatal critical care medicine and neurology. Given the complexity of both the medical and neurological problems seen in newborn babies, a shared management model that combines neonatology and neurology teams, such as that used in our institution, is desirable. At our center at the University of California, San Francisco, CA, USA, neurologists have an important role in the daily management of babies with acute and subacute neurological problems (Box 1), in interpretation of EEG and imaging studies, and in treatment decision-making and predictions of prognosis. An example of our co-management strategy for neonatal seizures is outlined in Box 2. A multidisciplinary neonatal neurological intensive care nursery working group formulates evidence-based protocols for the evaluation and management of neurological disorders that are common in newborn infants (Box 3). Although day-to-day bedside shared management might not be feasible at every center, specialists in neonatal neurocritical care (either neurologists or neonatologists) can formulate evidence-based guidelines for use in the institution and provide education for trainees and nursing staff. These efforts will improve awareness of acute neurological problems and facilitate the application of optimal neurocritical care.

Box 3 | Treatment and evaluation protocols for babies with neurological disorders

A selection of current protocols used at the UCSF NICN for the management of neurological disorders in neonates are listed below. The goal of these protocols is to facilitate consistent evidence-based evaluation and management of neonates with neurological disorders.

Hypothermia therapy for neonatal HIE
Passive and active therapy during transport to UCSF
Whole-body cooling after admission to UCSF NICN
- Standardized order set specific for patients receiving hypothermia therapy
- Standardized nursing assessment and care

Seizure therapy guidelines (see Box 1)

Brain monitoring protocols for:
Suspected seizures
Neonates at risk of seizures, such as those with critical illness, sepsis, respiratory failure, or metabolic disorders
Premature newborn babies <28 weeks' gestation

Evaluation of neonates with perinatal stroke

Indications for brain MRI in neonates
Babies born at <28 weeks' gestation are imaged at term-correct age
Infants with a critical illness, such as congenital diaphragmatic hernia, or after extracorporeal membrane oxygenation therapy
Infants with HIE (who should undergo MRI at 3–6 days of life to observe maximal changes in diffusion, as imaging findings at this time are predictive of outcome; most of these patients are discharged home before day 10 of life)
Infants with seizures (who should undergo MRI with DWI, MRA and MRV at 24–48 h after admission)

Abbreviations: DWI, diffusion-weighted imaging; HIE, hypoxic–ischemic encephalopathy; NICN, neonatal neurological intensive care nursery; MRA, magnetic resonance angiography; MRV, magnetic resonance venography; UCSF, University of California, San Francisco.

A new nursing focus

In the neonatal intensive care unit, the traditional focus of monitoring is on the cardiorespiratory systems, and each neonatal bed space contains equipment to monitor blood oxygenation, respiration, and cardiac function. Neonatal nurses are skilled at using these monitoring devices and are experts in caring for infants with compromised cardiopulmonary function. With the advent of hypothermia therapy and bedside monitoring of brain electrical activity, the integration of these new techniques into bedside neurological assessments and the involvement of nurses trained to analyze and interpret the data from these new technologies are critical to the provision of brain-focused care.

To understand the principles of neuroprotection and brain monitoring, nurses receive didactic education

(including lessons, lectures and training) in neuroanatomy, pathophysiology and basic electrophysiology. Nurses trained in neonatal neurocritical care, who can assess the severity of HIE, monitor and respond to physiological changes that occur during hypothermia, interpret the aEEG output, and rapidly alert the physician team regarding changes in the patient's neurological status, are crucial to the provision of specialized neurological care. In addition, nurses provide appropriate neurodevelopmental care to patients, including positioning that is appropriate for the maturational status of the patient, minimizing stimulation and painful procedures, and offering both information about the principles of neurocritical care and emotional support to families.

The benefits of providing developmentally appropriate and family-centered care of neonates have long been recognized, although the effect of this approach on long-term outcomes has been difficult to demonstrate.[99–101] Commonly employed practices include positioning, noise and stimulation reduction, clustering of nursing care to limit the number of contact episodes, and 'kangaroo' care (providing prolonged skin-to-skin contact to the newborn baby). The effects of complex developmental care interventions, such as the Neonatal Individualized Developmental Care and Assessment Program (NIDCAP), on short-term and long-term measures of outcome are controversial, as some trials show a benefit and others show no difference in outcomes.[102–104] Neonates included in a small randomized trial of NIDCAP demonstrated a positive correlation between use of NIDCAP and improved brain structure and function;[105] however, further work is needed in this area to support the widespread implementation of models of developmental care that are both time-intensive and staff-intensive.

Conclusions

Provision of neurological intensive care for newborn babies is a new paradigm in neonatal intensive care that requires further training of neonatal nurses, students, residents and fellows, as well as close collaboration between neonatologists, neurologists and neuroradiologists. Neurological intensive care of neonates applies principles learned from adult neurocritical care, such as the need for neurological evaluations and monitoring of brain activity. The current focus of research in this setting is on developing evidence-based protocols and guidelines for the management of acute neurological problems in newborn babies, adopting brain-protective strategies, and incorporating 'brain care' into the routine management of these patients. As therapies for brain injury continue to develop, and technologies used for brain monitoring, seizure detection and imaging continue to evolve, neonatal intensive care units will need to adapt and implement the principles of focused neurological care into their daily practice.

Review criteria

Articles selected for inclusion in this Review were identified from the authors' personal libraries on neurological neonatal intensive care, seizure management, and mechanisms of brain injury and neuroprotection in neonates. In addition, we performed a PubMed search for seminal articles in neonatal neurological care over the past two decades using the following keywords: "neonatal seizures", "MRI", "aEEG", "neuroprotection", "neurocritical care", and "developmental care". We also examined the bibliographies of retrieved articles to identify additional relevant papers.

1. Hintz, S. R., Kendrick, D. E., Vohr, B. R., Poole, W. K. & Higgins, R. D. Changes in neurodevelopmental outcomes at 18 to 22 months' corrected age among infants of less than 25 weeks' gestational age born in 1993–1999. *Pediatrics* **115**, 1645–1651 (2005).
2. Clark, S. L. & Hankins, G. D. Temporal and demographic trends in cerebral palsy—fact and fiction. *Am. J. Obstet. Gynecol.* **188**, 628–633 (2003).
3. Miller, S. P. & Ferriero, D. M. From selective vulnerability to connectivity: insights from newborn brain imaging. *Trends Neurosci.* **32**, 496–505 (2009).
4. Back, S. A., Riddle, A. & McClure, M. M. Maturation-dependent vulnerability of perinatal white matter in premature birth. *Stroke* **38**, 724–730 (2007).
5. Whitelaw, A. *et al.* Randomized clinical trial of prevention of hydrocephalus after intraventricular hemorrhage in preterm infants: brain-washing versus tapping fluid. *Pediatrics* **119**, e1071–e1078 (2007).
6. Edwards, A. D. *et al.* Neurological outcomes at 18 months of age after moderate hypothermia for perinatal hypoxic ischaemic encephalopathy: synthesis and meta-analysis of trial data. *BMJ* **340**, c363 (2010).
7. Perlman, J. M. *et al.* Part 11: Neonatal resuscitation: 2010 International Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science With Treatment Recommendations. *Circulation* **122**, S516–S538 (2010).
8. Azzopardi, D. Clinical management of the baby with hypoxic ischaemic encephalopathy. *Early Hum. Dev.* **86**, 345–350 (2010).
9. Stola, A. & Perlman, J. Post-resuscitation strategies to avoid ongoing injury following intrapartum hypoxia-ischemia. *Semin. Fetal Neonatal Med.* **13**, 424–431 (2008).
10. Gonzalez, F. F., Fang, A. & Ferriero, D. M. Is erythropoietin the answer? *Pediatr. Res.* **69**, 2–3 (2011).
11. Chang, Y. S. *et al.* Erythropoietin improves functional and histological outcome in neonatal stroke. *Pediatr. Res.* **58**, 106–111 (2005).
12. Gonzalez, F. F. *et al.* Erythropoietin sustains cognitive function and brain volume after neonatal stroke. *Dev. Neurosci.* **31**, 403–411 (2009).
13. Wen, T. C. *et al.* Gender differences in long-term beneficial effects of erythropoietin given after neonatal stroke in postnatal day-7 rats. *Neuroscience* **139**, 803–811 (2006).
14. Sun, Y., Calvert, J. W. & Zhang, J. H. Neonatal hypoxia/ischemia is associated with decreased inflammatory mediators after erythropoietin administration. *Stroke* **36**, 1672–1678 (2005).
15. Osredkar, D., Sall, J. W., Bickler, P. E. & Ferriero, D. M. Erythropoietin promotes hippocampal neurogenesis in in-vitro models of neonatal stroke. *Neurobiol. Dis.* **38**, 259–265 (2010).
16. Aher, S. & Ohlsson, A. Late erythropoietin for preventing red blood cell transfusion in preterm and/or low birth weight infants. *Cochrane Database of Systematic Reviews*, Issue 3. Art. No.: CD004868. doi:10.1002/14651858.CD004868.pub2 (2006).
17. Juul, S. E. *et al.* A phase I/II trial of high-dose erythropoietin in extremely low birth weight infants: pharmacokinetics and safety. *Pediatrics* **122**, 383–391 (2008).
18. Elmahdy, H. *et al.* Human recombinant erythropoietin in asphyxia neonatorum: pilot trial. *Pediatrics* **125**, e1135–e1142 (2010).
19. Zhu, C. *et al.* Erythropoietin improved neurologic outcomes in newborns with hypoxic-ischemic encephalopathy. *Pediatrics* **124**, e218–e226 (2009).
20. Faulkner, S. *et al.* Xenon augmented hypothermia reduces early lactate/*N*-acetylaspartate and cell death in perinatal asphyxia. *Ann. Neurol.* doi:10.1002/ana.22387.
21. Ma, J. & Zhang, G. Y. Lithium reduced *N*-methyl-D-aspartate receptor subunit 2A tyrosine phosphorylation and its interactions with Src and Fyn mediated by PSD-95 in rat hippocampus following cerebral ischemia. *Neurosci. Lett.* **348**, 185–189 (2003).
22. Dinse, A. *et al.* Xenon reduces glutamate-, AMPA-, and kainate-induced membrane currents

in cortical neurones. *Br. J. Anaesth.* **94**, 479–485 (2005).
23. Gruss, M. *et al.* Two-pore-domain K^+ channels are a novel target for the anesthetic gases xenon, nitrous oxide, and cyclopropane. *Mol. Pharmacol.* **65**, 443–452 (2004).
24. Ma, D. *et al.* Xenon and hypothermia combine to provide neuroprotection from neonatal asphyxia. *Ann. Neurol.* **58**, 182–193 (2005).
25. Hobbs, C. *et al.* Xenon and hypothermia combine additively, offering long-term functional and histopathologic neuroprotection after neonatal hypoxia/ischemia. *Stroke* **39**, 1307–1313 (2008).
26. Neuroprotective effects of hypothermia combined with inhaled xenon following perinatal asphyxia (TOBYXe). *ClinicalTrials.gov* [online], http://clinicaltrials.gov/ct2/show/results/NCT00934700 (2009).
27. Jatana, M., Singh, I., Singh, A. K. & Jenkins, D. Combination of systemic hypothermia and *N*-acetylcysteine attenuates hypoxic-ischemic brain injury in neonatal rats. *Pediatr. Res.* **59**, 684–689 (2006).
28. Husson, I. *et al.* Melatoninergic neuroprotection of the murine periventricular white matter against neonatal excitotoxic challenge. *Ann. Neurol.* **51**, 82–92 (2002).
29. Welin, A. K. *et al.* Melatonin reduces inflammation and cell death in white matter in the mid-gestation fetal sheep following umbilical cord occlusion. *Pediatr. Res.* **61**, 153–158 (2007).
30. Hutton, L. C., Abbass, M., Dickinson, H., Ireland, Z. & Walker, D. W. Neuroprotective properties of melatonin in a model of birth asphyxia in the spiny mouse (*Acomys cahirinus*). *Dev. Neurosci.* **31**, 437–451 (2009).
31. Bouslama, M. *et al.* Melatonin prevents learning disorders in brain-lesioned newborn mice. *Neuroscience* **150**, 712–719 (2007).
32. Olivier, P. *et al.* Melatonin promotes oligodendroglial maturation of injured white matter in neonatal rats. *PLoS ONE* **4**, e7218 (2009).
33. Kelen, D. & Robertson, N. J. Experimental treatments for hypoxic ischaemic encephalopathy. *Early Hum. Dev.* **86**, 369–377 (2010).
34. Lynch, J. K. Epidemiology and classification of perinatal stroke. *Semin. Fetal Neonatal Med.* **14**, 245–249 (2009).
35. Kersbergen, K. J. *et al.* Anticoagulation therapy and imaging in neonates with a unilateral thalamic hemorrhage due to cerebral sinovenous thrombosis. *Stroke* **40**, 2754–2760 (2009).
36. Brouwer, M. J. *et al.* Ultrasound measurements of the lateral ventricles in neonates: why, how and when? A systematic review. *Acta Paediatr.* **99**, 1298–1306 (2010).
37. Gonzalez, F. F. & Ferriero, D. M. Neuroprotection in the newborn infant. *Clin. Perinatol.* **36**, 859–880 (2009).
38. Miller, S. P. *et al.* Seizure-associated brain injury in term newborns with perinatal asphyxia. *Neurology* **58**, 542–548 (2002).
39. Bartha, A. I. *et al.* Neonatal seizures: multicenter variability in current treatment practices. *Pediatr. Neurol.* **37**, 85–90 (2007).
40. Bittigau, P. *et al.* Antiepileptic drugs and apoptotic neurodegeneration in the developing brain. *Proc. Natl Acad. Sci.* **99**, 15089–15094 (2002).
41. Painter, M. J. *et al.* Phenobarbital compared with phenytoin for the treatment of neonatal seizures. *N. Engl. J. Med.* **341**, 485–489 (1999).
42. Barks, J. D., Liu, Y. Q., Shangguan, Y. & Silverstein, F. S. Phenobarbital augments hypothermic neuroprotection. *Pediatr. Res.* **67**, 532–537 (2010).
43. Meyn, D. F. Jr, Ness, J., Ambalavanan, N. & Carlo, W. A. Prophylactic phenobarbital and whole-body cooling for neonatal hypoxic-ischemic encephalopathy. *J. Pediatr.* **157**, 334–336 (2010).
44. Sarkar, S. *et al.* Does phenobarbital improve the effectiveness of therapeutic hypothermia in infants with hypoxic-ischemic encephalopathy? *J. Perinatol*. doi:jp.10.1038.2011.41.
45. Liu, Y., Barks, J. D., Xu, G. & Silverstein, F. S. Topiramate extends the therapeutic window for hypothermia-mediated neuroprotection after stroke in neonatal rats. *Stroke* **35**, 1460–1465 (2004).
46. Herrero, A. I., Del Olmo, N., Gonzalez-Escalada, J. R. & Solis, J. M. Two new actions of topiramate: inhibition of depolarizing $GABA_A$-mediated responses and activation of a potassium conductance. *Neuropharmacology* **42**, 210–220 (2002).
47. Filippi, L. *et al.* Topiramate concentrations in neonates treated with prolonged whole body hypothermia for hypoxic ischemic encephalopathy. *Epilepsia* **50**, 2355–2361 (2009).
48. Cilio, M. R. & Ferriero, D. M. Synergistic neuroprotective therapies with hypothermia. *Semin. Fetal Neonatal Med.* **15**, 293–298 (2010).
49. Kim, J. S., Kondratyev, A., Tomita, Y. & Gale, K. Neurodevelopmental impact of antiepileptic drugs and seizures in the immature brain. *Epilepsia* **48** (Suppl. 5), 19–26 (2007).
50. Maynard, D., Prior, P. F. & Scott, D. F. A continuous monitoring device for cerebral activity. *Electroencephalogr. Clin. Neurophysiol.* **27**, 672–673 (1969).
51. Bjerre, I., Hellstrom-Westas, L., Rosen, I. & Svenningsen, N. Monitoring of cerebral function after severe asphyxia in infancy. *Arch. Dis. Child.* **58**, 997–1002 (1983).
52. Hellstrom-Westas, L. & Rosen, I. Continuous brain-function monitoring: state of the art in clinical practice. *Semin. Fetal Neonatal Med.* **11**, 503–511 (2006).
53. Holmes, G. *et al.* Prognostic value of the electroencephalogram in neonatal asphyxia. *Electroencephalogr. Clin. Neurophysiol.* **53**, 60–72 (1982).
54. Biagioni, E. *et al.* Combined use of electroencephalogram and magnetic resonance imaging in full-term neonates with acute encephalopathy. *Pediatrics* **107**, 461–468 (2001).
55. Hellstrom-Westas, L., Rosen, I. & Svenningsen, N. W. Predictive value of early continuous amplitude integrated EEG recordings on outcome after severe birth asphyxia in full term infants. *Arch. Dis. Child. Fetal Neonatal Ed.* **72**, F34–F38 (1995).
56. Toet, M. C., Hellstrom-Westas, L., Groenendaal, F., Eken, P. & de Vries, L. S. Amplitude integrated EEG 3 and 6 hours after birth in full term neonates with hypoxic-ischaemic encephalopathy. *Arch. Dis. Child. Fetal Neonatal Ed.* **81**, F19–F23 (1999).
57. van Rooij, L. G. *et al.* Recovery of amplitude integrated electroencephalographic background patterns within 24 hours of perinatal asphyxia. *Arch. Dis. Child. Fetal Neonatal Ed.* **90**, F245–F251 (2005).
58. Osredkar, D. *et al.* Sleep-wake cycling on amplitude-integrated electroencephalography in term newborns with hypoxic-ischemic encephalopathy. *Pediatrics* **115**, 327–332 (2005).
59. Thoresen, M., Hellstrom-Westas, L., Liu, X. & de Vries, L. S. Effect of hypothermia on amplitude-integrated electroencephalogram in infants with asphyxia. *Pediatrics* **126**, e131–e139 (2010).
60. Nash, K. B. *et al.* Video-EEG monitoring in newborns with hypoxic-ischemic encephalopathy treated with hypothermia. *Neurology* **76**, 556–562 (2011).
61. Gunn, A. J. *et al.* Therapeutic hypothermia changes the prognostic value of clinical evaluation of neonatal encephalopathy. *J. Pediatr.* **152**, 55–58, 58 e51 (2008).
62. Toet, M. C., Lemmers, P. M., van Schelven, L. J. & van Bel, F. Cerebral oxygenation and electrical activity after birth asphyxia: their relation to outcome. *Pediatrics* **117**, 333–339 (2006).
63. Malone, A. *et al.* Interobserver agreement in neonatal seizure identification. *Epilepsia* **50**, 2097–2101 (2009).
64. Jensen, F. E. Neonatal seizures: an update on mechanisms and management. *Clin. Perinatol* **36**, 881–900, vii (2009).
65. Holmes, G. L. & Ben-Ari, Y. Seizures in the developing brain: perhaps not so benign after all. *Neuron* **21**, 1231–1234 (1998).
66. Holmes, G. L. & Ben-Ari, Y. The neurobiology and consequences of epilepsy in the developing brain. *Pediatr. Res.* **49**, 320–325 (2001).
67. van Rooij, L. G. *et al.* Effect of treatment of subclinical neonatal seizures detected with aEEG: randomized, controlled trial. *Pediatrics* **125**, e358–e366 (2010).
68. Garfinkle, J. & Shevell, M. I. Cerebral palsy, developmental delay, and epilepsy after neonatal seizures. *Pediatr. Neurol.* **44**, 88–96 (2011).
69. Bjorkman, S. T., Miller, S. M., Rose, S. E., Burke, C. & Colditz, P. B. Seizures are associated with brain injury severity in a neonatal model of hypoxia-ischemia. *Neuroscience* **166**, 157–167 (2010).
70. Glass, H. C. *et al.* Clinical neonatal seizures are independently associated with outcome in infants at risk for hypoxic-ischemic brain injury. *J. Pediatr.* **155**, 318–323 (2009).
71. van Wezel-Meijler, G., Steggerda, S. J. & Leijser, L. M. Cranial ultrasonography in neonates: role and limitations. *Semin. Perinatol* **34**, 28–38 (2010).
72. El-Dib, M., Massaro, A. N., Bulas, D. & Aly, H. Neuroimaging and neurodevelopmental outcome of premature infants. *Am. J. Perinatol* **27**, 803–818 (2010).
73. van Wezel-Meijler, G. *et al.* Magnetic resonance imaging of the brain in newborn infants: practical aspects. *Early Hum. Dev.* **85**, 85–92 (2009).
74. Dumoulin, C. L. *et al.* Magnetic resonance imaging compatible neonate incubator. *Magn. Reson. Engineering* **15**, 117–128 (2002).
75. Mathur, A. M., Neil, J. J., McKinstry, R. C. & Inder, T. E. Transport, monitoring, and successful brain MR imaging in unsedated neonates. *Pediatr. Radiol.* **38**, 260–264 (2008).
76. Rutherford, M. A. *et al.* Magnetic resonance imaging of white matter diseases of prematurity. *Neuroradiology* **52**, 505–521 (2010).
77. Shah, D. K. *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.* **153**, 170–175 (2008).
78. Glass, H. C. *et al.* Recurrent postnatal infections are associated with progressive white matter injury in premature infants. *Pediatrics* **122**, 299–305 (2008).

79. Anjari, M. *et al.* The association of lung disease with cerebral white matter abnormalities in preterm infants. *Pediatrics* **124**, 268–276 (2009).
80. Bonifacio, S. L. *et al.* Extreme premature birth is not associated with impaired development of brain microstructure. *J. Pediatr.* **157**, 726–732.e1 (2010).
81. Schmidt, B. *et al.* Long-term effects of caffeine therapy for apnea of prematurity. *N. Engl. J. Med.* **357**, 1893–1902 (2007).
82. Doyle, L. W. *et al.* Caffeine and brain development in very preterm infants. *Ann. Neurol.* **68**, 734–742 (2010).
83. Thayyil, S. *et al.* Cerebral magnetic resonance biomarkers in neonatal encephalopathy: a meta-analysis. *Pediatrics* **125**, e382–e395 (2010).
84. Azzopardi, D. & Edwards, A. D. Magnetic resonance biomarkers of neuroprotective effects in infants with hypoxic ischemic encephalopathy. *Semin. Fetal Neonatal Med.* **15**, 261–269 (2010).
85. Wartenberg, K. E. *et al.* Impact of medical complications on outcome after subarachnoid hemorrhage. *Crit. Care Med.* **34**, 617–623 (2006).
86. Diez-Tejedor, E. & Fuentes, B. Acute care in stroke: the importance of early intervention to achieve better brain protection. *Cerebrovascular Diseases* **17** (Suppl. 1), 130–137 (2004).
87. Mirski, M. A., Chang, C. W. & Cowan, R. Impact of a neuroscience intensive care unit on neurosurgical patient outcomes and cost of care: evidence-based support for an intensivist-directed specialty ICU model of care. *J. Neurosurg. Anesthesiol.* **13**, 83–92 (2001).
88. Suarez, J. I. Outcome in neurocritical care: advances in monitoring and treatment and effect of a specialized neurocritical care team. *Crit. Care Med.* **34**, S232–S238 (2006).
89. Varelas, P. N. *et al.* Impact of a neurointensivist on outcomes in patients with head trauma treated in a neurosciences intensive care unit. *J. Neurosurg.* **104**, 713–719 (2006).
90. Diringer, M. N. & Edwards, D. F. Admission to a neurologic/neurosurgical intensive care unit is associated with reduced mortality rate after intracerebral hemorrhage. *Crit. Care Med.* **29**, 635–640 (2001).
91. Solomon, R. A., Mayer, S. A. & Tarmey, J. J. Relationship between the volume of craniotomies for cerebral aneurysm performed at New York state hospitals and in-hospital mortality. *Stroke* **27**, 13–17 (1996).
92. Berman, M. F., Solomon, R. A., Mayer, S. A., Johnston, S. C. & Yung, P. P. Impact of hospital-related factors on outcome after treatment of cerebral aneurysms. *Stroke* **34**, 2200–2207 (2003).
93. Patel, H. C. *et al.* Specialist neurocritical care and outcome from head injury. *Intensive Care Med.* **28**, 547–553 (2002).
94. Elf, K., Nilsson, P. & Enblad, P. Outcome after traumatic brain injury improved by an organized secondary insult program and standardized neurointensive care. *Crit. Care Med.* **30**, 2129–2134 (2002).
95. Clayton, T. J., Nelson, R. J. & Manara, A. R. Reduction in mortality from severe head injury following introduction of a protocol for intensive care management. *Br. J. Anaesth.* **93**, 761–767 (2004).
96. Organised inpatient (stroke unit) care for stroke. *Cochrane Database of Systematic Reviews*, Issue 4. Art. No.: CD000197. doi:10.1002/14651858.CD000197.pub2 (2007).
97. Glass, H. C. *et al.* Neurocritical care for neonates. *Neurocrit. Care* **12**, 421–429 (2010).
98. McQuillen, P. S. & Miller, S. P. Congenital heart disease and brain development. *Ann. NY Acad. Sci.* **1184**, 68–86 (2010).
99. Lester, B. M. *et al.* Infant neurobehavioral development. *Semin. Perinatol.* **35**, 8–19 (2011).
100. Bustani, P. C. Developmental care: does it make a difference? *Arch. Dis. Child. Fetal Neonatal Ed.* **93**, F317–F321 (2008).
101. Conde-Agudelo, A., Belizan, J. M. & Diaz-Rossello, J. Kangaroo mother care to reduce morbidity and mortality in low birthweight infants. *Cochrane Database of Systematic Reviews*, Issue 3. Art. No.: CD002771. doi:10.1002/14651858.CD002771.pub2 (2011).
102. Maguire, C. M. *et al.* Effects of individualized developmental care in a randomized trial of preterm infants <32 weeks. *Pediatrics* **124**, 1021–1030 (2009).
103. Peters, K. L. *et al.* Improvement of short- and long-term outcomes for very low birth weight infants: Edmonton NIDCAP trial. *Pediatrics* **124**, 1009–1020 (2009).
104. McAnulty, G. B. *et al.* Effects of the Newborn Individualized Developmental *Care* and Assessment Program (NIDCAP) at age 8 years: preliminary data. *Clin. Pediatr. (Phila.)* **49**, 258–270 (2009).
105. Als, H. *et al.* Early experience alters brain function and structure. *Pediatrics* **113**, 846–857 (2004).

Author contributions

D. M. Ferriero, H. C. Glass, S. Peloquin and S. L. Bonifacio contributed equally to researching data for the article, writing the article, and review and/or editing of the manuscript before submission.