REVIEW OPEN

Reducing neurodevelopmental disorders and disability through research and interventions

Michael J. Boivin[1,2], Angelina M. Kakooza[3], Benjamin C. Warf[4], Leslie L. Davidson[5,6] & Elena L. Grigorenko[7]

We define neurodevelopment as the dynamic inter-relationship between genetic, brain, cognitive, emotional and behavioural processes across the developmental lifespan. Significant and persistent disruption to this dynamic process through environmental and genetic risk can lead to neurodevelopmental disorders and disability. Research designed to ameliorate neurodevelopmental disorders in low- and middle-income countries, as well as globally, will benefit enormously from the ongoing advances in understanding their genetic and epigenetic causes, as modified by environment and culture. We provide examples of advances in the prevention and treatment of, and the rehabilitation of those with, neurodevelopment disorders in low- and middle-income countries, along with opportunities for further strategic research initiatives. Our examples are not the only possibilities for strategic research, but they illustrate problems that, when solved, could have a considerable impact in low-resource settings. In each instance, research in low- and middle-income countries led to innovations in identification, surveillance and treatment of a neurodevelopmental disorder. These innovations have also been integrated with genotypic mapping of neurodevelopmental disorders, forming important preventative and rehabilitative interventions with the potential for high impact. These advances will ultimately allow us to understand how epigenetic influences shape neurodevelopmental risk and resilience over time and across populations. Clearly, the most strategic areas of research opportunity involve cross-disciplinary integration at the intersection between the environment, brain or behaviour neurodevelopment, and genetic and epigenetic science. At these junctions a robust integrative cross-disciplinary scientific approach is catalysing the creation of technologies and interventions for old problems. Such approaches will enable us to achieve and sustain the United Nations moral and legal mandate for child health and full development as a basic global human right.

Nature 527, S155–S160 (19 November 2015), DOI: 10.1038/nature16029

One evaluation of early childhood developmental status in low- and middle-income countries (LMICs) estimates that 15.7% of children are significantly delayed in their cognitive development, 26.3% in socioemotional development and 36.8% in either or both (D. C. McCoy, personal communication). Stunting, low wealth and living in a rural area are significantly associated with neurodevelopmental delay; most of the children live in Africa and eastern Asia. Fortunately, neurodevelopmental science is benefitting from rapidly expanding technologies for the integration of the environmental (for example, infectious disease, nutritional and carer quality), brain-related (for example, developmental neuroscience and brain imaging) and genetic (for example, epigenetic modelling and genomic big data) domains that drive neurodevelopment. Figure 1 illustrates the mutually interactive nature of these three developmental domains, along with the current strategic areas of research at the environment–brain–gene interface (Box 1).

Advances in developmental science have triggered a reconceptualization of neurodevelopment based on the recognition that developmental processes are a part of child health in the broader context of communicable and non-communicable disease[1]. The developmental origins of the health and disease hypothesis proposes that the physiological processes of developmental plasticity operate in early childhood, but have the potential for adverse consequences in later life[2]. Consequently, childhood — particularly early childhood — is a high-priority target for both preventive and remediating interventions to address the pervasive developmental needs in LMICs (D. C. McCoy, personal communication).

In this Review, we describe several high-impact findings that have emerged from research in low-resource settings that pertain to the developmental milieu of the child, its relationship to the brain and behavioural neurodevelopmental integrity of the child (neurodevelopmental disorders), and the genetic and epigenetic underpinnings that can drive this relationship. As we review key scientific advances in each of these three domains, we propose strategic areas of ongoing and future research that could provide innovative models to fuel significant

[1]Department of Psychiatry, College of Osteopathic Medicine, 965 Fee Road, East Fee Hall Room 225, Michigan State University, East Lansing, Michigan 48824, USA. [2]International Neurologic and Psychiatric Epidemiology Program (INPEP), West Fee Hall Room 321, Michigan State University, East Lansing, Michigan 48824-1315, USA. [3]Department of Paediatrics and Child Health, School of Medicine, Makerere University College of Health Sciences, PO Box 7072, Kampala, Uganda. [4]Boston Children's Hospital, Department of Neurosurgery, 300 Longwood Avenue, Hunnewell, 2nd Floor, Boston, Massachusetts 02115, USA. [5]Department of Epidemiology, Mailman School of Public Health, College of Physicians and Surgeons at the Columbia University Medical Center, 722 West 168 Street 1613, New York, New York 10032, USA. [6]Department of Pediatrics, College of Physicians and Surgeons at the Columbia University Medical Center, 722 West 168 Street 1613, New York, New York 10032, USA. [7]Yale Child Study Center, Department of Psychology, Department of Epidemiology and Public Health, Yale University, PO Box 207900, 230 South Frontage Road, New Haven, Connecticut 06520-7900, USA. Correspondence should be addressed to M. J. B. e-mail: boivin@msu.edu.

advances and evidence-based interventions for meeting the developmental needs of children. We conclude by summarizing ways in which this model (environment, brain and gene) provides rich opportunities for a more global approach to child-development science, making it possible to achieve the UNICEF mandate of full child health and development for all[3,4].

APPROACHES TO MALARIA

In 2013 there were around 198 million cases of malaria of which 584,000 resulted in death[5]. A child dies from malaria every minute, and one in four survivors present with significant neurodevelopmental impairment[6,7]. However, cognitive rehabilitation, speech and physical therapy, and carer-training interventions can improve cognitive performance and behaviour of treated mother–child pairs[8,9]. As rehabilitation approaches are evaluated, there is mounting evidence of the neurocognitive benefits of computerized cognitive rehabilitation training (CCRT) in African children with a brain injury as a result of severe malaria and in those with HIV-related brain injury[10]. Dissemination and implementation science must now inform innovative approaches to bring such interventions to scale in low-resource communities. Mobile network health (mHealth) research opportunities are a high priority, given the ever-increasing access that children and adolescents in low-resource settings have to mobile-based internet and computing technologies[11]. Another key strategic research opportunity is to evaluate the impact of neurocognitive rehabilitation interventions such as CCRT, on the enhancement of brain-development neuroprotective factors[12,13] (Box 2). We can then evaluate the extent to which such brain-based biomarkers mediate the neuropsychological benefits of CCRT, along with how neurocognitive rehabilitative interventions diminish biomarkers of brain inflammation (such as tumour necrosis factor-α (TNF-α) and creatinine).

APPROACHES TO PAEDIATRIC HIV

Globally, roughly 3.4 million children live with HIV infection and are at high risk of significant neurodevelopmental disabilities. Of these, almost 90% live in Africa where only 24% of infected children have access to anti-retroviral (ARV) treatment[14]. These children's environmental risk factors are compounded by poor nutrition owing to protein and specific micronutrient deficiencies[15]. They also often have parasitic, respiratory and enteric diarrheal infections[16]. Such compounded risk exists whether a child is infected with HIV (proximal risk) or lives in a household or community where HIV has a persisting and significant disruptive impact (distal risk)[17]. Multifaceted risk for all kinds of early developmental insults (for example, infection, malnutrition and poverty) demands that children in low-resource communities need a comprehensive package of assessments and interventions to holistically enhance their development[16].

Recent epigenetic evidence suggests that chronic poverty may 'shrink' children's brains over successive generations as documented by longitudinal multigeneration brain-imaging research[18]. These considerations justify the junction between the environment and the brain as a highly strategic point of intervention. This is further illustrated by the strategic importance of implementation-science research in designing an effective comprehensive package of services for antenatal and postnatal care. This is evident when considering at-risk adolescent mothers in LMICs and the heightened risk of neurodisability in their infants. Pregnancy in adolescence is associated with premature delivery, stillbirth, fetal distress, birth asphyxia, low birth weight and miscarriage[19]. Furthermore, if the adolescent mother is also suffering from malnutrition these risks are compounded for the infant — long-term effects as a consequence of low birth weight include stunting, poor neurodevelopmental outcomes, and increased susceptibility to cardiovascular and metabolic diseases such as obesity and diabetes[20]. In fact, there is evidence that environmental factors such as nutrition can alter epigenetic modifications and thus play a part in the development of these disorders later in life[21]. The maternal microbiome is also important to infant health outcomes, including the risk of pre-term birth, the development of gastrointestinal diseases such as irritable bowel syndrome, and the development of the immune system[22].

One of the greatest public health initiatives developed in the modern era of infectious disease is the prevention of mother-to-child transmission (PMTCT) of HIV. These interventions have reduced perinatal infection of children born to infected mothers from more than 30% to less than 1%[23]. However, there are still gestational neurodevelopmental risks associated with early exposure to ARVs[24]. One of the most exciting developments in the treatment of HIV has been the development and anti-retroviral characterization of VRC01. This is a potent and broadly neutralizing anti-HIV monoclonal antibody that prevents HIV-1 transmission from plasmacytoid dendritic cells to CD4 T lymphocytes[25]. Once proven safe for infants, such therapies should be administered as soon as possible after the diagnosis of HIV in infants, and the long-term neurodevelopmental and neurocognitive protective benefits of such innovative treatment strategies should be evaluated. These therapies could also be effective in the prevention of HIV transmission.

TRAUMA-ASSOCIATED PSYCHIATRIC ILLNESS

Another strategic research opportunity is to further evaluate how maternal depression is associated with widespread changes in DNA methylation in their offspring[26,27]. Such epigenetic processes can result in heightened risk of depression and anxiety disorders in children as they become adults[28]. How best to package and bring to scale a strategic set of intervention services that address this remains a neglected area in high-impact implementation science. Likewise, populations traumatized through conflict and genocide can pass on psychiatric disorders transgenerationally. This may be partly mediated by the hormonal effects of maternal stress on neuropsychiatric risk for children *in utero* in regions where women have been traumatized through sexual violence in conflict zones (glucocorticoid-mediated inducement of cytokine inflammatory responses causing methylation of DNA in children *in utero*). Such intergenerational epigenetic mechanisms of psychiatric disorders necessitate evidence-based and sustainable community-wide treatment strategies to address these disorders within the foundational mother–child caring fabric of that society[29]. Task shifting will be a crucial strategy in addressing such community mental health support services[30,31]. There is evidence to support the effectiveness of a year-long maternal carer training programme for children who are affected by HIV in rural Uganda to facilitate child development in low-resource settings, while remediating maternal depression and enhancing carer functionality[8,11].

NODDING SYNDROME

The beginning of the millennium was marked by the manifestation of the enigmatic condition nodding syndrome, which affects school-age children, and is reported in South Sudan, northern Uganda and southern Tanzania. This condition is characterized by episodes of repetitive nodding (dropping forward of the head) often coupled with seizure-like behaviours (for example, convulsions or staring spells) that occur during attempted feeding[32,33]. Nodding syndrome is also characterized by stunted brain growth, including significant brain atrophy near the hippocampal and glia matter of the brain and significant cerebellar involvement. This is accompanied by lifelong profound neurodisability, severe behavioural problems and high mortality[34].

The nodding is caused by an atonic seizure, but the aetiology of this seizure is unknown, although associations with other developmental conditions have been established. Nodding syndrome is most prevalent in areas with high infection rates of the parasitic worm *Onchocerca volvulus* — a nematode carried by black fly of the genus *Simulium* — the bites of which can cause onchocerciasis, a highly prevalent type of blindness caused by infection. Other reports suggest an association between the syndrome and malnutrition[35]. Future research of this

syndrome must focus on understanding the aetiology so that it can be prevented, diagnosed early and treated effectively. Emerging diseases that profoundly affect children, such as nodding syndrome, provide an important opportunity for developing diagnostic, management and intervention techniques adapted to LMICs that, in turn, can be used for the prevention of worldwide outbreaks of diseases that lead to severe disability.

Although nodding disease is highly localized, such enigmatic disorders that arise from time-to-time and result in profound neurodisability are important because they reveal the urgent need to develop scientific models that can be seamlessly integrated into emerging disciplines. These include geographical ecological mapping, maps of parasitology dispersion, genotypic mapping across populations and their geographical dispersions, and geographically mapped epidemiological risk of infectious disease. These multi-layered models must then be integrated with neuropathogenic mechanism models that include sensitive and specific brain inflammatory markers, as well as the corresponding neuropsychological sequelae of such central nervous system inflammatory markers.

MALNUTRITION AND DISEASE

Childhood malnutrition, both through prenatal and perinatal maternal micronutrient deficiencies[36], infant micronutrient deficiencies[37], and protein–calorie deficiency, imposes a heavy burden on neurodevelopment[38–40]. The primary effects of malnutrition have been associated with elevated mortality, morbidity, and risk of cognitive and socioemotional impairment. Although it has been extensively researched, and interventions have been attempted, malnutrition remains a serious challenge to children's development in LMICs. Efforts have not yet succeeded in eliminating malnutrition or in successfully bringing interventions to scale[41]. Secondary effects of malnutrition are associated with vulnerability to microbial pathogens that can also severely disrupt neurodevelopment[42,43].

Enteric infections

The aetiology of malnutrition is complex. In particular, malnutrition might result from enteric infections of bacteria that are highly prevalent in LMICs, and include both well-known (*Escherichia coli*, *Vibrio cholerae*, and species of *Salmonella*, *Shigella* and anaerobic streptococci)[44] and emerging pathogens (enteroaggregative *E. coli*, *Cryptosporidium* and *Giardia*)[45]. These infections can significantly affect childhood brain or behavioural development, presumably through damage to the gut microbiota. This can lead to intestinal inflammation that diminishes intestinal absorption, and protein and micronutrient deficiencies compounded by recurring dehydration and malaise[46,47]. This field of research has also significantly advanced our understanding of the inter-relationships between genetics (for example, neuroprotective *APOE* polymorphisms), enteric diseases, nutritional malabsorption and neurodevelopment in young children[48,49].

An important research opportunity provided by this work involves the clinical evaluation of the neurodevelopmental benefits of micronutrient interventions to enteric disease, including whether glutamine works better than glucose as a key ingredient of oral rehydration and repair therapy (ORRT)[50]. Glutamate intervention may be more effective in the repair of intestinal barrier functions and hence improve child development as well as the absorption of ARV drugs in children with HIV.

Food-borne neurotoxins and nutritional malabsorption

Konzo disease is a permanent, irreversible, upper-motor neuron disorder, occurring primarily in rural areas of sub-Saharan Africa that are dependent on bitter varieties of cassava (*Manihot esculenta*; an annual crop cultivated for its edible starchy tuberous root, which is a major source of carbohydrates and, therefore, a food staple). Epidemiological studies have documented konzo outbreaks — mostly in women and children — in periods of food insecurity that have been brought about by drought, displacement by war or conflict, or other factors that have led to the insufficient processing of cassava tubers. The insufficient breakdown of linamarin compounds that contain cyanide result in neurological damage and seem to lead to outbreaks of konzo, which has been documented mostly in the Congo, Central African Republic, Mozambique and Tanzania[51–53] with a prevalence of between 0.1% and 17% in affected villages[54]. Studies have recently documented neurocognitive impairments in children with konzo. Furthermore, even children who do not show signs of konzo, but who live in konzo-affected households may have neurocognitive impairment of working memory and learning ability[55].

Konzo offers an important opportunity for integrative neurodevelopmental science. Neuroinflammatory markers of brain injury from

BOX 1 | STRATEGIC ONGOING AND IMMINENT RESEARCH OPPORTUNITIES

Strategic ongoing and imminent research opportunities at the intersection between brain, gene and environment (Fig. 1), which potentially lead to neurodisability interventions in low- and middle-income countries.

Gene and brain — ongoing research opportunities

- Neural tube defects with associated hydrocephalus and developmental brain anomalies.
- Monogenic disorders (either heritable or *de novo*) for which neurodevelopmental disorders are caused by various types of mutations (from a point mutation such as in sickle cell disease to in a single gene such as in Rett syndrome).
- Disorders due to alterations in the mitochondrial genome (for example, creatine deficiency syndromes).
- Neurodevelopmental disability of unknown origin such as autism spectrum disorders, specific learning disabilities, attention deficit hyperactivity disorder and conduct disorders.

Environment and brain — ongoing and imminent (shown by *) research opportunities

- Brain injury from central nervous system infections related to neonatal sepsis (meningitis, ventriculitis and cerebritis) and resulting post-infectious hydrocephalus.
- Toxic exposure of cyanide to young children fed cassava as a result of food insecurity and insufficient processing of cassava with high linamarin content.
- *Evaluate neurocognitive rehabilitation interventions on brain development neuroprotective factors and on biomarkers of brain inflammation (for example, TNF-α and creatinine).
- *Hormonal effects of maternal stress on child neuropsychiatric risk *in utero* for mothers in LMICs who have been traumatized through sexual violence in conflict zones (glucocorticoid-mediated inducer of the cytokine inflammatory responses).
- *Chronic poverty may 'shrink' brains over successive generations as documented by magnetic resonance imaging research.

Environment and gene — imminent research opportunities

- Maternal depression is associated with widespread changes in DNA methylation in their offspring that may persist into adulthood for exposed children.
- Genetic vulnerability to onchocerciasis may lead to neuroinflammation, seizures, and profound neurodisability in the form of nodding disease in select vulnerable populations in regions highly endemic for onchocerciasis.
- Genetic factors related to why asymptomatic positive malaria parasitaemia progresses to cerebral malaria (or severe malaria anaemia) in African children with subsequent brain injury.
- *APOE* and neuroprotection for enteric diseases (with elevated risk for age-associated dementia types).

cyanide toxicity and inflammatory markers of microbiota destruction in the gut from cyanide toxicity need to be mapped on sensitive neurocognitive impairment indicators in children. Konzo offers a rare opportunity to test integrative models of nutritional toxicity in the brain and gut against a backdrop of malnutrition and corresponding micronutrient deficiencies. Gauging their comparative weighting in the mediation of neurodevelopmental disability within the cognitive and neuromotor domains will allow us to determine the effectiveness of prevention and treatment strategies. Since konzo is entirely preventable, health education and promotion intervention methods should be evaluated at the community-wide level in terms of the benefit to disability-adjusted life years[56].

TREATING HYDROCEPHALUS IN LMICS

Hydrocephalus, the abnormal accumulation of cerebrospinal fluid in the cerebral ventricles, has multiple causes, and is especially prevalent in LMICs. Failure to treat the condition almost always leads to death or severe neurodevelopmental disability. Higher birth rates and limited perinatal care contribute to a greater burden of care for hydrocephalus in LMICs[57] (for example, there are 100,000–250,000 new infant cases of hydrocephalus annually in sub-Saharan Africa alone[41]). In addition to the expected burden of congenital hydrocephalus in LMICs, climate-driven neonatal ventriculitis of unknown pathogenesis has recently been identified as one of the chief causes of infant hydrocephalus (60% of cases in Uganda)[58–61]. In sub-Saharan Africa, rates of neonatal sepsis are estimated to be 170 per 1,000 births, with a corresponding mortality of 10 deaths per 1,000 births[62]. For survivors with post-infectious hydrocephalus (PIH), neurodevelopmental consequences of the primary brain injury can be devastating even before hydrocephalus develops. One-third of those with PIH remain profoundly disabled at five years, even after successful surgery[63]. However, innovative surgical techniques have been pioneered and developed in Uganda that have revolutionized the treatment of hydrocephalus worldwide[63–65].

The standard treatment for hydrocephalus has long been the implantation of tubing that drains cerebrospinal fluid from the ventricles to the peritoneal cavity (ventriculoperitoneal shunt). However, this treatment creates lifelong dependence on an unreliable implanted device that often requires an emergency operation when it fails (40% failure within 2 years of the original implantation)[66]. An effective, minimally invasive treatment method (endoscopic third ventriculostomy (ETV) combined with endoscopic choroid plexus cauterization (CPC)) that avoids shunt-dependence in most infants was developed in Uganda as an alternative[65]. The procedure — the safety and efficacy of which were demonstrated initially in LMICs and then in high-income countries[65] — combines two techniques. These involve creating a new opening through the floor of the third ventricle and reducing the choroid plexus tissue in the lateral ventricles by cauterization. Building the capacity to achieve universal access to optimal and affordable hydrocephalus treatment for infants in LMICs is an ongoing challenge[64]. Present efforts involve task shifting by training non-physician medical officers to undertake the shunt placement, allowing neurosurgeons to focus on the more complex third ventriculostomy procedures. Dissemination and implementation research is needed to test the effectiveness of this task-shifting approach.

GENETIC STUDIES OF NEURODEVELOPMENT

The genome has a substantial role in the aetiology of neurodevelopmental disorders. These disorders can be classified into six major categories (Box 2). There is abundant evidence that the disorders in all six categories may affect many facets of child development. The disorders in categories 1–3 are typically severe and impose multiple developmental challenges from birth. These conditions are referred to as congenital conditions (their broad definition also includes conditions that result from various challenges in pregnancy, such as severe micronutrient deficiency, for example folate deficiency). Given what is known about the prevalence of these conditions in high-income countries, estimates suggest that at least 7.6 million children are born annually with severe congenital conditions, and that the number is especially high in LMICs[67].

BOX 2 | SIX GENETIC CAUSES OF NEURODISABILITY IN CHILDREN

1. Disorders caused by specific genomic lesions (either heritable or arising *de novo*).
2. Monogenic disorders (either heritable or *de novo*) for which the disorders are caused by various types of mutations (from a point mutation, such as sickle cell disease, to repeat expansion) in a single gene (for example, mutations in the *MECP2* gene in Rett syndrome and a number of CGG repeats in the *FMR1* gene in fragile X syndrome).
3. Disorders due to alterations in the mitochondrial genome (for example, creatine deficiency syndromes).
4. Relatively common disorders such as autism spectrum disorders, specific learning disabilities, attention-deficit hyperactivity disorder and conduct disorders.
5. Disorders triggered by the environment, but the burden of which is controlled by the genome.
6. Conditions that arise from the involvement of the epigenome (modifications in the function of the genome that are not caused by any structural alterations in the genome itself).

The disorders in categories 4–6 include common multifactorial conditions with onset in early childhood. Of note, less than 50% of countries have policies for the control of these conditions[67]. These conditions currently constitute a substantial health challenge in high-income countries, but are substantially understudied, under diagnosed and underserved in LMICs. Although limited, the relevant research in LMICs unfolds in a number of dimensions, converging around the understanding that economic development and changes in lifestyle have led, or are leading to, a rapid increase in the observed prevalence of these multifactorial disorders. In other words, as people's environment improves, the role and prominence of genetic and genomic factors will increase. Common disorders include conditions that are attributable to epigenetic influences[68] (for example, DNA methylation and histone modification).

In this context, two epigenetic mechanisms have been highlighted. The first mechanism connects nutritional challenges to the manifestation of metabolic syndromes. This happens through a causal link between nutrient restrictions *in utero* and in early childhood, lack of clean water and sanitation, and high levels of infectious organisms in the environment. These can lead to epigenetic changes in pathways related to metabolism, blood pressure and glucose regulation[69]. The second mechanism is the link between psychological stress and the glucocorticoid-mediated inducer of the cytokine inflammatory response[70]. Both exemplify the developmental origins of the health-and-disease hypothesis and its relevance to the aetiology of neurodevelopmental disability in LMICs[71].

Key research and training priorities related to these six disorder categories are: determining their global prevalence; training scientists in appropriate molecular technologies and sustaining this increased human-resource capacity by providing ongoing support and training to keep up with the rapid technological advances in the field; developing methods for cheap and reliable diagnoses of the widest possible range of congenital conditions and identification of the broadest possible range of risk factors for complex multifactorial disorders; developing practical, accessible and inexpensive procedures for family-planning counselling (preconception and post-delivery); and continuing to build the capacity and infrastructure needed to initiate cutting-edge, relevant research that is comparable with that taking place in high-income countries. These research and training priorities should translate

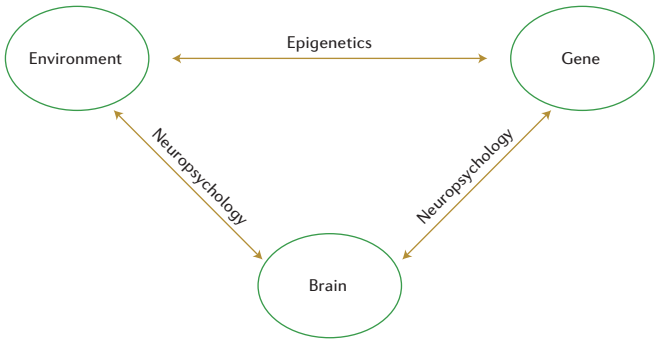

Figure 1 | Mutually interactive domains — environment, gene and brain — interact in terms of environment–gene socioevolutionary processes (epigenetic), environment–brain moment-by-moment neurocognition (neuropsychology), and gene–brain universal brain and behavioural processes in child neurodevelopment. The foundation for this multi-level interaction is brain plasticity as shaped by risk and resilience in child neurodevelopment, which occurs at the evolutionary (physical environment), cultural (social environment), individual (brain) and neuronal genotype (genetic) levels. The most strategic points of research opportunity as presented in this Review occur at the intersections between brain, gene and environment.

into public health services that can help couples in family planning and the resource mobilization needed to nurture children with such disorders.

CONCLUSION

We have outlined significant scientific findings and challenges that have emerged from research in LMICs. We have provided strategic research examples and areas of research opportunity (aetiology and intervention) at the junction between the environment, brain and gene. The dynamic interactions among these three domains are at the foundation of brain neurodevelopment in children (Box 1). New technologies are providing ever more sensitive biomarkers that can be related to the brain and behavioural neurodevelopmental integrity of the child. New technologies are also emerging that link the regional and global surveillance of neurodisability to environmental risk, and these can be integrated with the genetic and epigenetic underpinnings that drive this relationship.

Future approaches must accommodate the use of new data gathered by innovative technologies, offering fresh approaches to old problems in child development in LMICs. These new approaches will prove to be especially strategic at the points of interface and integration between the environment, gene and brain (Fig. 1). New models that can effectively integrate these three domains into a comprehensive and cohesive paradigm must have the following hallmarks.

Interdisciplinary approaches

Research in LMICs needs to take into account the complex multifactorial causes of neurodisability (Fig. 1). Environmental risk from natural disasters, social unrest, poverty and infection can offset a child's neurodevelopmental trajectory at the points of interface between gene and brain, during the antenatal and postnatal stages of development. In addition to toxins from the diet such as cassava-based cyanide in konzo, environmental toxins from mining and biomass fuels are leading to levels of exposure that can affect child neurodevelopment across entire communities. These complex systems of developmental risk factors call for comprehensive interdisciplinary approaches to understand the developmental trajectories so as to identify children at serious risk of neurodisability and those in need of intervention in LMICs. For example, maternal health programmes need to work closely with early childhood programmes to ensure an optimal prenatal environment for the developing foetus, improved pregnancy outcomes, and effective parental and community-wide interventions to enhance child development. Another example is the engagement of parents in child-awareness programmes to facilitate their cognitive and socioemotional development. We have cited examples of specific family-based[72] and community-based[73] interventions that have been successfully used in LMICs. Such interventions involve the integration of anthropology, public health education and promotion, social and media science, and developmental paediatric research.

Employment of new technologies

New technologies are enhancing research approaches in LMICs, presenting enormous potential to transform health-care delivery. The development of new mobile technologies for surveillance, assessment and treatment are particularly needed in LMICs, where mobile phone ownership is rapidly rising. Computerized interventions are already being used for the treatment of children with cerebral malaria and HIV. New and improved surgical techniques will be crucial for saving lives and altering atypical developmental trajectories. The miniaturization of diagnostic technologies that provide data for integrative risk maps, which can be integrated at the population level with genome distributions, will allow for effective population surveillance and public health intervention at a community-wide level.

Implementation research

Research in LMICs cannot be divorced from the health systems and the cultural context in which the populations are situated. Research on the implementation of evidence-based prevention and intervention is needed. Scientifically sound interventions scaled up to the community and national level will require working with governmental and non-governmental partners to ensure sustainability. As already noted, significant advances have been made by 'task shifting' in resource-constrained settings in order to, for example, delegate health-care tasks to health workers with lower qualifications. Such strategies have shown especially promising results in dealing with mental health gaps, but can be effectively applied for the rehabilitative care of neurodisability in children[74]. Task-shifting strategies, however, need to be evaluated for approaches within dissemination and implementation science. It is only in this manner that we will achieve the UN moral and legal mandate of full childhood neurodevelopment as a basic human right for all.

1. UN General Assembly. *Political Declaration of the High-level Meeting of the General Assembly on the Prevention and Control of Non-communicable Diseases* http://www.who.int/nmh/events/un_ncd_summit2011/political_declaration_en.pdf (United Nations, 2012).
2. Gluckman, P. *The Developmental Origins of Health and Disease* (Springer, 2006).
3. UNICEF. *The State of the World's Children: Children with Disabilities* (UNICEF, 2013).
4. United Nations. *Road Map Towards the Implementation of the United Nations Millennium Declaration. Report No. A56/326* (UN, 2002).
5. World Health Organization. *The World Malaria Report* (WHO, 2014).
6. Boivin, M. J. *et al.* Cognitive impairment after cerebral malaria in children: a prospective study. *Pediatrics* **119,** e360–e366 (2007).
7. John, C. C. *et al.* Cerebral malaria in children is associated with long-term cognitive impairment. *Pediatrics* **122,** e92–e99 (2008).
8. Boivin, M. J. *et al.* A year-long caregiver training program improves cognition in preschool Ugandan children with human immunodeficiency virus. *J. Pediatr.* **163,** 1409–1416 (2013).
9. Boivin, M. J. *et al.* A year-long caregiver training program to improve neurocognition in preschool Ugandan HIV-exposed children. *J. Dev. Behav. Pediatr.* **34,** 269–278 (2013).
10. Bangirana, P., Boivin, M. J. & Giordani, B. in *Neuropsychology of Children in Africa: Perspectives on Risk and Resilience* Vol. 1 (eds Boivin, M. J. & Giordani, B.) 277–298 (Springer, 2013).
11. Boivin, M. J. & Giordani, B. in *Cultural Neuroscience: Cultural Influences on Brain Function.* Vol. 178 (ed Chiao, J. Y.) 113–135 (Elsevier, 2009).
12. Brett, Z. H. *et al.* A neurogenetics approach to defining differential susceptibility to institutional care. *Int. J. Behav. Dev.* **39,** 150–160 (2015).
13. Croen, L. A. *et al.* Brain-derived neurotrophic factor and autism: maternal and infant peripheral blood levels in the Early Markers for Autism (EMA) study. *Autism Res.* **1,** 130–137 (2008).
14. UNAIDS. *UNAIDS Report on the Global AIDS Epidemic 2010* (UN, 2013).
15. Laughton, B., Cornell, M., Boivin, M. & Van Rie, A. Neurodevelopment in perinatally HIV-infected children: a concern for adolescence. *J. Int. AIDS Soc.* **16,** 18603 (2013).
16. Kvalsvig, J. D., Taylor, M., Kauchali, S. & Chhagan, M. in *Neuropsychology of Children in Africa: Perspectives on Risk and Resilience* (eds Boivin, M. J. & Giordani, B) Ch. 3, 37–67 (Springer, 2013).

17. Baral, S., Logie, C. H., Grosso, A., Wirtz, A. L. & Beyrer, C. Modified social ecological model: a tool to guide the assessment of the risks and risk contexts of HIV epidemics. *BMC Public Health* **13,** 482 (2013).
18. Noble, K. G. *et al.* Family income, parental education and brain structure in children and adolescents. *Nature Neurosci.* **18,** 773–778 (2015).
19. Reichman, N. E. & Kenney, G. M. Prenatal care, birth outcomes and newborn hospitalization costs: patterns among Hispanics in New Jersey. *Family Plan. Perspect.* **30,** 182–187 (1998).
20. Dewey, K. G. & Begum, K. Long-term consequences of stunting in early life. *Matern. Child Nutr.* **7** (Suppl 3), 5–18 (2011).
21. Kubota, T., Miyake, K., Hariya, N. & Mochizuki, K. Understanding the epigenetics of neurodevelopmental disorders and DOHaD. *J. Dev. Origins Health Dis.* **6,** 96–104 (2015).
22. Gregory, K. E. Microbiome aspects of perinatal and neonatal health. *J. Perinat. Neonatal Nurs.* **25,** 158–162 (2011).
23. National Institutes of Health. *NIH-sponsored Study Identifies Superior Drug Regimen for Preventing Mother-to-Child HIV Transmission* http://www.nih.gov/news/health/nov2014/niaid-17.htm (NIH, 2014).
24. Sirois, P. A. *et al.* Safety of perinatal exposure to antiretroviral medications: developmental outcomes in infants. *Pediatr. Infect. Dis. J.* **32**, 648–655 (2013).
25. Guo, D., Shi, X., Song, D. & Zhang, L. Persistence of VRC01-resistant HIV-1 during antiretroviral therapy. *Sci. China. Life Sci.* **57**, 88–96 (2014).
26. Braithwaite, E. C., Kundakovic, M., Ramchandani, P. G., Murphy, S. E. & Champagne, F. A. Maternal prenatal depressive symptoms predict infant *NR3C1* 1F and *BDNF* IV DNA methylation. *Epigenetics* **10**, 408–417 (2015).
27. Murgatroyd, C., Quinn, J. P., Sharp, H. M., Pickles, A. & Hill, J. Effects of prenatal and postnatal depression, and maternal stroking, at the glucocorticoid receptor gene. *Transl. Psychiatry* **5,** e560 (2015).
28. Nemoda, Z. *et al.* Maternal depression is associated with DNA methylation changes in cord blood T lymphocytes and adult hippocampi. *Transl. Psychiatry* **5,** e545 (2015).
29. Perroud, N. *et al.* The Tutsi genocide and transgenerational transmission of maternal stress: epigenetics and biology of the HPA axis. *World J. Biol. Psychiatry* **15,** 334–345 (2014).
30. Nelson, R. Combating global health worker shortages: task shifting and sharing may provide one solution. *Am. J. Nursing* **112,** 17–18 (2012).
31. Swartz, L., Kilian, S., Twesigye, J., Attah, D. & Chiliza, B. Language, culture, and task shifting — an emerging challenge for global mental health. *Glob. Health Action* **7,** 23433 (2014).
32. Foltz, J. L. *et al.* An epidemiologic investigation of potential risk factors for nodding syndrome in Kitgum District, Uganda. *PLoS ONE* **8,** e66419 (2013).
33. Sejvar, J. J. *et al.* Clinical, neurological, and electrophysiological features of nodding syndrome in Kitgum, Uganda: an observational case series. *Lancet Neurol.* **12,** 166–174 (2013).
34. Couper, J. Prevalence of childhood disability in rural KwaZulu-Natal. *S. Afr. Med. J.* **92,** 549–552 (2002).
35. Idro, R. *et al.* Nodding syndrome in Ugandan children—clinical features, brain imaging and complications: a case series. *BMJ Open* **3,** e002540 (2013).
36. Koura, K. G. *et al.* Usefulness of child development assessments for low-resource settings in francophone Africa. *J. Dev. Behav. Pediatr.* **34,** 486–493 (2013).
37. Lozoff, B. *et al.* Long-lasting neural and behavioral effects of iron deficiency in infancy. *Nutr. Rev.* **64**, S34–S43 (2006).
38. Abubakar, A., Holding, P., Newton, C. R., van Baar, A. & van de Vijver, F. J. The role of weight for age and disease stage in poor psychomotor outcome of HIV-infected children in Kilifi, Kenya. *Dev. Med. Child Neurol.* **51**, 968–973 (2009).
39. Abubakar, A., Holding, P., Van de Vijver, F. J., Newton, C. & Van Baar, A. Children at risk for developmental delay can be recognised by stunting, being underweight, ill health, little maternal schooling or high gravidity. *J. Child Psychol. Psychiatry* **51**, 652–659 (2009).
40. Abubakar, A. *et al.* Socioeconomic status, anthropometric status, and psychomotor development of Kenyan children from resource-limited settings: a path-analytic study. *Early Hum. Dev.* **84**, 613–621 (2008).
41. Abubakar, A. in *Neuropsychology of Children in Africa: Perspectives on Risk and Resilience* (eds Boivin, M. J. & Giordani, B.) Ch. 9, 181–202 (Springer, 2013).
42. Sinclair, D., Abba, K., Grobler, L. & Sudarsanam, T. D. Nutritional supplements for people being treated for active tuberculosis. *Cochrane Database Syst. Rev.* **9,** CD006086 (2011).
43. Thankachan, P. *et al. Helicobacter pylori* infection does not influence the efficacy of iron and vitamin B12 fortification in marginally nourished Indian children. *Eur. J. Clin. Nutr.* **64,** 1101–1107 (2010).
44. Guerrant, R. L. *et al.* Mechanisms and impact of enteric infections. *Adv. Exp. Med. Biol.* **473,** 103–112 (1999).
45. Guerrant, R. L., Oria, R. B., Moore, S. R., Oria, M. O. & Lima, A. A. Malnutrition as an enteric infectious disease with long-term effects on child development. *Nutrition Rev.* **66,** 487–505 (2008).
46. Guerrant, R. L., Lima, A. A. & Davidson, F. Micronutrients and infection: interactions and implications with enteric and other infections and future priorities. *J. Infect. Dis.* **182,** S134–S138 (2000).
47. Guerrant, D. I. *et al.* Association of early childhood diarrhea and cryptosporidiosis with impaired physical fitness and cognitive function four-seven years later in a poor urban community in northeast Brazil. *Am. J. Trop. Med. Hyg.* **61,** 707–713 (1999).
48. Oria, R. B., Patrick, P. D., Blackman, J. A., Lima, A. A. & Guerrant, R. L. Role of apolipoprotein E4 in protecting children against early childhood diarrhea outcomes and implications for later development. *Med. Hypotheses* **68,** 1099–1107 (2007).
49. Oria, R. B. *et al.* APOE4 protects the cognitive development in children with heavy diarrhea burdens in Northeast Brazil. *Pediatr. Res.* **57,** 310–316 (2005).
50. Mitter, S. S. *et al.* Apolipoprotein E4 influences growth and cognitive responses to micronutrient supplementation in shantytown children from northeast Brazil. *Clinics* **67,** 11–18 (2012).
51. Cliff, J. *et al.* Konzo associated with war in Mozambique. *Trop. Med. Int. Health* **2,** 1068–1074 (1997).
52. Tylleskar, T. *et al.* Konzo: a distinct disease entity with selective upper motor neuron damage. *J. Neurol. Neurosurg. Psychiatry* **56,** 638–643 (1993).
53. Tylleskar, T., Legue, F. D., Peterson, S., Kpizingui, E. & Stecker, P. Konzo in the Central African Republic. *Neurology* **44,** 959–961 (1994).
54. Banea, J. P. *et al.* Survey of the konzo prevalence of village people and their nutrition in Kwilu District, Bandundu Province, DRC. *Afr. J. Food Sci.* **9,** 43–50 (2015).
55. Boivin, M. J. *et al.* Neuropsychological effects of konzo: a neuromotor disease associated with poorly processed cassava. *Pediatrics* **131**, e1231–e1239 (2013).
56. Bradbury, J. H., Cliff, J. & Denton, I. C. Uptake of wetting method in Africa to reduce cyanide poisoning and konzo from cassava. *Food Chem. Toxicol.* **49,** 539–542 (2010).
57. Warf, B. C. & the East African Neurosurgery Research Consortium. Pediatric hydrocephalus in East Africa: prevalence, causes, treatments, and strategies for the future. *World Neurosurg.* **73,** 296–300 (2010).
58. Kiwanuka, J. *et al.* The microbial spectrum of neonatal sepsis in Uganda: recovery of culturable bacteria in mother-infant pairs. *PLoS ONE* **8,** e72775 (2013).
59. Li, L. *et al.* Association of bacteria with hydrocephalus in Ugandan infants. *J. Neurosurg. Pediatr.* **7,** 73–87 (2011).
60. Schiff, S. J., Ranjeva, S. L., Sauer, T. D. & Warf, B. C. Rainfall drives hydrocephalus in East Africa. *J. Neurosurg. Pediatr.* **10,** 161–167 (2012).
61. Warf, B. C. Hydrocephalus in Uganda: the predominance of infectious origin and primary management with endoscopic third ventriculostomy. *J. Neurosurg.* **102,** 1–15 (2005).
62. Thaver, D. & Zaidi, A. K. Burden of neonatal infections in developing countries: a review of evidence from community-based studies. *Pediatric Infect. Dis. J.* **28,** S3–S9 (2009).
63. Warf, B. C., Dagi, A. R., Kaaya, B. N. & Schiff, S. J. Five-year survival and outcome of treatment for postinfectious hydrocephalus in Ugandan infants. *J. Neurosurg. Pediatr.* **8,** 502–508 (2011).
64. Warf, B. C. *et al.* Costs and benefits of neurosurgical intervention for infant hydrocephalus in sub-Saharan Africa. *J. Neurosurg. Pediatr.* **8,** 509–521 (2011).
65. Stone, S. S. & Warf, B. C. Combined endoscopic third ventriculostomy and choroid plexus cauterization as primary treatment for infant hydrocephalus: a prospective North American series. *J. Neurosurg. Pediatr.* **14,** 439–446 (2014).
66. Kulkarni, A. V. *et al.* Outcomes of CSF shunting in children: comparison of Hydrocephalus Clinical Research Network cohort with historical controls: clinical article. *J. Neurosurgery Pediatr.* **12,** 334–338 (2013).
67. Alwan, A. & Modell, B. Recommendations for introducing genetics services in developing countries. *Nature Rev. Genetics* **4,** 61–68 (2003).
68. DeBoer, M. D. *et al.* Early childhood growth failure and the developmental origins of adult disease: do enteric infections and malnutrition increase risk for the metabolic syndrome? *Nutrition Rev.* **70,** 642–653 (2012).
69. Tobi, E. W. *et al.* DNA methylation differences after exposure to prenatal famine are common and timing- and sex-specific. *Human Mol. Gen.* **18,** 4046–4053 (2009).
70. McCall, C. E., El Gazzar, M., Liu, T., Vachharajani, V. & Yoza, B. Epigenetics, bioenergetics, and microRNA coordinate gene-specific reprogramming during acute systemic inflammation. *J. Leukocyte Biol.* **90,** 439–446 (2011).
71. Fernald, L. C., Grantham-McGregor, S. M., Manandhar, D. S. & Costello, A. Salivary cortisol and heart rate in stunted and nonstunted Nepalese school child. *Eur. J. Clin. Nutrition* **57,** 1458–1465 (2003).
72. Elder, J. P. *et al.* Caregiver behavior change for child survival and development in low- and middle-income countries: an examination of the evidence. *J. Health Commun.* **19,** S25–S66 (2014).
73. Farnsworth, S. K. *et al.* Community engagement to enhance child survival and early development in low- and middle-income countries: an evidence review. *J. Health Commun.* **19,** S67–S88 (2014).
74. Mendenhall, E. *et al.* Acceptability and feasibility of using non-specialist health workers to deliver mental health care: stakeholder perceptions from the PRIME district sites in Ethiopia, India, Nepal, South Africa, and Uganda. *Soc. Sci. Med.* **118,** 33–42 (2014).

ACKNOWLEDGEMENTS

The authors thank N. Anand, K. Michels, D. Silberberg and D. Krotoski for their editorial oversight, substantive input, guidance and support in this Review. I. Familiar-Lopez and H. Ruiseñor-Escudero provided help with Figure 1 and editorial comments for the final drafts and references as postdoctoral research associates for M.J.B. B. Giordani and V. Kutlesic provided advice and support to M. J. B. during the manuscript development process.

COMPETING FINANCIAL INTERESTS

The authors declare no competing financial interests. Financial support for publication has been provided by the Fogarty International Center.

ADDITIONAL INFORMATION