

INTRODUCTION **OPEN**

Brain and other nervous system disorders across the lifespan — global challenges and opportunities

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This is an exciting time for scientific discovery that aims to reduce the frequency and impact of neurological, mental health and substance-use disorders. As it became increasingly clear that low- and middle-income countries have a disproportionate share of these disorders, and that many of the problems are best addressed by indigenous researchers who can seek context-sensitive solutions, the US National Institutes of Health and other research funders began to invest more in low- and middle-income country-focused research and research capacity-building to confront this significant public health challenge. In an effort to identify existing information, knowledge gaps, and emerging research and research capacity-building opportunities that are particularly relevant to low- and middle-income countries, in February 2014 the Center for Global Health Studies at the National Institutes of Health Fogarty International Center held a workshop to explore these issues with scientific experts from low- and middle-income countries and the United States. This evolved into the preparation of the Reviews in this supplement, which is designed to highlight opportunities and challenges associated with topical areas in brain-disorders research over the coming decade. This Introduction highlights some of the over-arching and intersecting priorities for addressing causes, prevention, treatment and rehabilitation as well as best practices to promote overall nervous system health. We review some brain disorders in low- and middle-income countries, while the Reviews describe relevant issues and the epidemiology of particular conditions in greater depth.

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The proportion of the global burden of disease (GBD) that is attributable to neurological, mental health, developmental and substance-use (NMDS) disorders is expected to rise worldwide, partly because of the projected increase in the number of individuals reaching the age at which they are at risk of onset of many of these disorders^{1,2}. This rise will be steeper in low- and middle-income countries (LMICs) given the long-term effects of early life trauma, infectious disease and malnutrition, which contribute to the development of these disorders that in turn lead to early death or a lifetime of disability. Despite their significant contribution to the burden of disease and disability, NMDS disorders have been largely absent from the global health research agenda, and LMICs have insufficient capacity to address them. The past two decades have witnessed increased attention to, and investments in, NMDS issues. However, given the rising burden of NMDS disorders worldwide and opportunities to build on scientific advances while strengthening LMIC research capacity, we are at a crucial juncture in moving this agenda forward. This is a time to reflect on and use what we have learned to confront existing, and prepare for future, challenges. We hope that the research and research capacity-building priorities discussed in this collection will help to galvanize action to confront the rising tide of brain and other nervous system disorders.

INTERNATIONAL HEALTH COMMUNITY RECOGNITION

Before the publication of the World Bank's 1993 seminal Annual

Report, *Investing in Health*, neurological, psychiatric, developmental and substance-use disorders in LMICs were considered unusual, difficult to understand and a low priority for research investment. The 1993 report, based largely on the first studies of the global burden of disease³, has since been refined and progressively updated. Prior to the implementation of measures such as the disability-adjusted life year (DALY; Table 1), the global burden of disease was primarily quantified in terms of mortality. With the advent of the DALY, the importance of neurological and psychiatric disorders became evident, accounting for approximately 28% of the global burden of disease. Subsequently, the US Institute of Medicine called for the need to direct research resources towards addressing NMDS disorders in LMICs⁴ in its 2001 study and report, *Neurological, Psychiatric and Developmental Disorders — Meeting the Challenge in the Developing World*. This report not only encapsulated a growing body of evidence regarding the impact of brain disorders, but it also provided the seed for a new initiative to support research and research training in global brain disorders: the *Brain Disorders in the Developing World: Research Across the Lifespan Program* (brain programme) supported by the National Institutes of Health (NIH) Fogarty International Center, several NIH Institute and Center partners, and other organizations (Box 1). Further impetus was added by inclusion of several chapters on NMDS disorders in the 2006 second edition of *Disease Control Priorities in Developing Countries*⁵.

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Table 1 | Proportions of age-standardized estimated disability adjusted life years (DALYs; >0.5%) attributable to all neurological, mental health and substance-use disorders by high-income and low- and middle-income countries (LMICs)

Disorder	Absolute DALYs* as global per thousand people (rank) †	Percentage in high-income countries (developed)	Percentage in low- and middle-income countries (developing)
NEUROLOGICAL SEQUELAE IN VARIOUS INFECTIOUS, SYSTEMIC AND CONGENITAL DISORDERS			
HIV/AIDS‡	130,900	1.19	3.67
All neglected tropical diseases and malaria‡	108,700	0.072	5.16
Nutritional deficiencies§	85,300 (3)	0.63	3.95
Low back pain	83,100 (1)	5.8	2.78
Neonatal encephalopathy (birth asphyxia/trauma)	50,150	0.33	2.33
Sensory organ diseases	34,700 (5)	1.68	1.35
Neck pain	33,640 (4)	2.24	1.14
Meningitis‡	29,400	0.13	1.38
Brain and nervous system cancers	6,100	0.53	0.19
Down's syndrome	1,775	0.8	1.71
NEUROLOGICAL DISORDERS: NON-COMMUNICABLE¶			
Cerebrovascular disease (all strokes)#	102,200	5.97	3.79
Neurological disorders (all)	73,800	4.42	2.71
Migraine	22,360 (6)	1.21	0.84
Epilepsy	17,400 (23)	0.44	0.75
Alzheimer's disease and other types of dementia	11,350 (21)	1.75	0.22
Other diagnosed neurological disorders	17,870	0.53	0.76
MENTAL HEALTH AND BEHAVIOURAL DISORDERS			
Mental health (all) **	185,200 (29)	11.1	6.73
Unipolar depressive disorders	74,260	4.01	2.81
Major depressive disorder	63,200 (2)	3.42	2.39
Anxiety disorders	26,830 (9)	1.6	0.98
Schizophrenia	15,000 (11)	0.85	0.49
Bipolar depressive disorders	12,870 (17)	0.63	0.5
Dysthymia	11,100 (16)	0.6	0.42
SUBSTANCE-USE DISORDERS††			
Drug-use disorders	20,000 (19)	1.53	0.67
Alcohol-use disorders	17,640 (22)	1.52	0.56
Total rate estimates (major categories with direct nervous-system involvement and >0.5% DALYs only in either a developed or developing region)	716,905	36.15	29.1

*DALY is defined as a measure of overall disease burden and expressed as the sum of years of potential life lost due to ill-health, disability or premature mortality. DALYs¹, listed high to low for each neurological, mental health and substance-use disorder type, for only those disorders with >0.5% rates in either high-income country or LMIC. Estimates for high-income countries were derived from the 'developed' region data whereas those for LMIC were from 'developing' region data¹. †Ranked as disorders among the top 25 causes of global years lived with disability (YLDs)¹². ‡Conduct disorder was foremost. ‡Includes cerebral malaria, encephalitis and HIV dementia. §Includes hearing and vision loss, including macular degeneration. ||Iron-deficiency anaemia is key. ¶Non-communicable neurological disorders include types of dementia, Parkinson's disease and related disorders, epilepsy, multiple sclerosis, migraine, tension-type headache and other neurological disorders. #Includes both ischaemic (70–80%) and haemorrhagic strokes (20–30%). **Mental health includes major depressive disorder, dysthymia, unipolar and bipolar depressive disorders, schizophrenia, anxiety disorders, eating disorders, autism, Asperger's syndrome, attention deficit hyperactivity disorder, conduct disorder, idiopathic intellectual disability and other mental and behavioural disorders. ††Substance-use disorders include alcohol, opioid, cocaine, amphetamines, cannabis and other drug use.

Subsequently, The Grand Challenges Canada – Saving Brains and Global Mental Health, The EU Tropical Diseases Research Program, the UK Wellcome Trust, the UK Medical Research Council and others have joined to support global research and training to address brain disorders in LMICs (Fig. 1). Despite the successes and investments from these efforts and the willing support from numerous partners, including the US Agency for Overseas Development and the Bill and Melinda Gates Foundation, the implications of the burden of NMDs disorders in LMICs remains insufficiently addressed by appropriate policies and research and capacity-building investments. As we analyse these important ventures (Fig. 1), there are clearly several geographical gaps in investment, concerns for the extent of overlap in research funding for certain countries, and the potential for partnerships between funders and between countries.

BURDEN AND RANGE OF NERVOUS-SYSTEM DISORDERS

With the advent of the DALY, the importance of neurological and psychiatric disorders was undeniable; by 2010 all causes of NMDs disorders, including stroke, were estimated to account for more than 29% of the GBD (Table 1). In tandem with increased life expectancy⁶, the GBD has shifted from premature death to increased years lived in disability per 100,000. Not surprisingly, as the GBD has continued to move in the direction of non-communicable diseases, the burden of mental health and substance-use disorders has increased by around 40% in the past two decades⁷. Non-communicable diseases have been found to be the major cause of death and disability (Table 1), it is therefore time to include them as crucial priorities for research and policy initiatives in LMICs.

Although our appreciation of the importance of NMDs has matured significantly, serious contextual problems that obfuscate the true burden

BOX 1 | THE GLOBAL BRAIN PROGRAMME

Scope of, and data from, 2003 to 2013 National Institutes of Health/Fogarty International Center ongoing Global Brain programme¹¹.

- Support the development and conduct of innovative, collaborative research and research training projects, between developed and developing country scientists, on brain disorders throughout life, relevant to LMICs¹¹
- The research should include a lifespan approach, for example nutrition or early exposure with sequelae or impact throughout life
- The programme has created a global network of researchers in 45 countries
- Projects have informed policies and programmes at the national and international levels
- Grants have resulted in 435 peer-reviewed publications from 249 unique journals
- The programme has catalysed new research projects supported by other funders
- Outputs include new tools for clinical assessment in the LMIC context, laboratory tools and methods

of these disorders remain. By definition, disorders in the GBD classification are attributed to underlying causes rather than to clinical manifestations. Thus, for example, disabilities that result from neuropathies are attributed to diabetes or HIV. Similarly, among types of epilepsy, only idiopathic epilepsies are considered to be neurological burdens. Where an underlying cause for seizures is known or suspected (for example, traumatic brain injury), the GBD methodology attributes the epilepsy-associated disability to the underlying cause. Highest-ranked causes of death in the GBD 2010 study include several that are neurological in nature, for example stroke (ranked 2nd), malaria (ranked 11th), neonatal encephalopathy (ranked 24th) and meningitis (ranked 29th). All these conditions, none of which are included in the neurological category, rank similarly high in terms of their contributions to global disability⁸.

Neglected tropical disorders (NTD) are also disproportionately neurological in nature⁹. Three of the seventeen NTDs recognized by the World Health Organization (WHO) are primarily neurological infections (rabies, human African trypanosomiasis and leprosy) and, of the remaining NTDs, some of the more severe manifestations are the result of nervous-system involvement (central nervous system schistosomiasis and Chagas-related stroke). When these are considered in this context, the true estimate of DALYs that are accounted for by NMDs disorders would be substantially higher than 29% (Table 1).

Research undertaken since the US Decade of the Brain campaign in the 1990s has established that many of the most common and disabling neurological conditions are preventable or remedial with inexpensive therapies. Treatment for epilepsy and secondary stroke prevention are ranked by the World Bank among the ‘best buys’ in global health¹⁰. In the past decade, relatively small investments in scientific inquiry that are relevant to brain disorders in LMICs are yielding crucial insights, which are applicable to the broader global community. These findings also point the way to the intervention studies that should follow, which range from definitive clinical trials to population-level interventions targeting risk factors for NMDs disorders. Where research has pointed toward more optimal ways to structure medical education or provide health services, implementation with rigorous evaluations is needed and plans for a broad scale-up delineated.

Given this unique point in time, in February 2014 the Center for Global Health Studies at the Fogarty International Center held a workshop to explore the state of the science and to identify emerging research and research capacity-building priorities in brain disorders that are particularly relevant to LMICs. This evolved into the preparation of the Reviews in this collection, which is designed to highlight opportunities and challenges associated with specific topical areas in brain-disorders

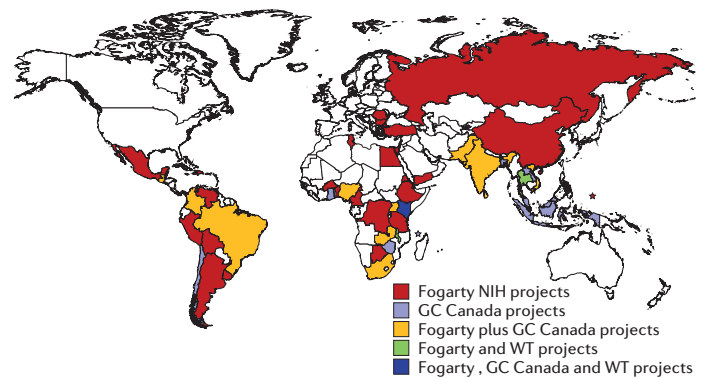


Figure 1 | Research support for neurological, mental health and substance-use (NMDs) disorders in low- and middle-income countries. Colour-coded distribution of concerted programmes from principal agencies that support (currently and during the past decade) projects on NMDs disorders. Further details can be obtained from the agency reports^{11,13}. There are numerous other organizations that support programmes that affect brain health, but that are not shown on this map. Fogarty, Fogarty International Center; GC Canada, Grand Challenges Canada — Saving Brains and Global Mental Health; WT, UK Wellcome Trust.

research in the coming decade, including causes, prevention, treatment and rehabilitation. We highlight some of the over-arching and intersecting priorities for addressing brain disorders in LMICs, and the subsequent Reviews describe these issues and the epidemiology of particular conditions in greater depth.

THEMES AND INTERSECTING RESEARCH APPROACHES

Despite financial and human-resource challenges, there have been many exciting discoveries related to NMDs disorders that have global implications. Examples include refinement of the classification of HIV/AIDS; realization of more substance-use disorders; definition of the sequelae of infectious diseases, seizure disorders and behavioural disorders; and identification of mechanisms of environmental toxicants in sub-Saharan Africa. Similarly, genetic studies associated with neurodegenerative disorders, for example Huntington’s disease and Alzheimer’s disease in Venezuela and Columbia have advanced our knowledge of diagnosis, risk factors and prospective treatments. Genetic and cognitive studies in Brazil are leading to interventions that may help to mitigate cognitive deficits in children owing to malnutrition.

The unique genetic makeup, environmental and traumatic exposures, infections, the local health system and nutritional challenges of diverse LMIC settings, mean that interventions and approaches that have been developed and tested in high-income country settings will often not be feasible or effective if simply transplanted to LMICs. In fact, solutions developed in LMICs may have global applications, such as new surgical techniques for children with incipient hydrocephalus developed in Uganda (see page S155) and may lead to a decrease or an elimination of disability caused by this condition, and perhaps cheaper and better treatments for children around the world. Thus, it is crucial that research be conducted in the environments in which the techniques are intended to be used. Several Reviews in this series provide examples of why this is the case in the context of brain disorders (for example, disorders associated with development, trauma, environment and adolescence). The conduct of high-quality research requires a cadre of in-country and well-trained scientists, and an adequately resourced research infrastructure that can support their research (see page S207). This series highlights priorities for research and research training that are related to specific diseases and conditions. We highlight overarching priorities included in these papers that cut across multiple disease areas (Box 2).

BOX 2 | PRIORITIES FOR DIFFERENT THEMES ACROSS MULTIPLE DISORDERS**Surveillance and epidemiology**

- Determination of prevalence and incidence of specific brain disorders, including in vulnerable populations
- Strengthening of reporting infrastructure, data quality and disease registries, and standardization of registries for country comparisons
- Use of statistical modelling where possible to inform resource allocation and implementation of interventions
- Prevalence of specific risk factors and measures of their impact among affected populations
- Better design of disease epidemiology that accurately captures incidence, type and duration of nervous system sequelae of infections and other conditions

Basic and clinical research

- Understanding the epigenetic effects on the nervous system resulting from malnutrition, infections, environmental exposures and psychosocial factors
- Better understanding of the influence of genetics and the genome on brain-disorder pathogenesis and progression
- Explore the relationship between an individual's and a population's microbiome and correlates with the presence of diverse disorders
- Understanding of pathways that lead to late onset of neurological disease owing to early exposures
- Advance understanding of gene–environment–brain interactions
- Assessment of risks and interactions of co-infections and co-morbidities
- Development of effective and feasible physical, occupational and cognitive rehabilitation interventions
- Creation of biobanking, including of brain tissues in LMICs.

Implementation science and health systems

- Engagement of diverse stakeholders (including decision makers and programme implementers) to facilitate uptake and scale-up of effective interventions
- Evaluation of task-sharing models to address health-care provider shortages and to help create efficiencies in the health-care system and facilitate the delivery of effective services
- Research on how best to scale-up interventions that have proven efficacious in smaller, controlled settings

Technology advancement

- Development and refinement of effective point-of-care diagnostic tools, particularly for genetic-based neurological disorders
- Development and testing of mobile-technology interventions to screen, diagnose and monitor treatment of brain disorders
- Development and implementation of low-cost tools and techniques for the treatment and rehabilitation of conditions arising from brain and other nervous-system trauma

Capacity-building and research-infrastructure needs

- More clinician–neuroscientist researchers and others who are trained to deliver appropriate care for patients with brain disorders and participate in conducting research
- Strengthen capacity in neuroethics
- Development of enhanced and culturally adaptable cognitive assessment and screening tools
- Increased laboratory capacity
- Increased access to electrodiagnostics, genomic sequencing and neuroimaging technologies

WHAT NEXT?

Resource constraints and the unique factors that people living in LMICs face impose a particularly onerous burden on these countries, where most of those with brain and other nervous-system disorders live. This burden significantly affects the ability of children and adolescents to thrive and live out their true potential, and the ability of young adults to be economically productive and support their families, as well as the opportunity for older adults to age in safe and nurturing settings. However, we may be at a tipping point for research related to global brain disorders. Over the past few decades, exciting basic science discoveries have been made, effective interventions have been developed and advances in technology have set the stage for a research agenda that can lead to unprecedented progress in this field. In addition, research capacity strengthening in LMICs and an opportunity for comparative studies of the markedly different environments that exist between high-income countries and LMICs will yield universally beneficial knowledge.

Reduction of disease and disability that are associated with brain and other nervous-system disorders over the next decade will demand increased engagement from, and collaboration among, the scientific community, research funding agencies, national governments, academic institutions, multilateral organizations, advocacy organizations and health providers to increase both research in LMICs and the indigenous research capacity. We need to build on current knowledge of overall neurological health, and improve the lives of those living with brain and other nervous system disorders at any stage of life.

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ADDITIONAL INFORMATION

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