

**The role of science in coping with
the grand challenges facing
humanity**

Philip Campbell, *Nature*

Inter-Academy Panel Triennial

Rio de Janeiro

24 February 2013

Grand challenges in and beyond science

I want to highlight four topics of immediate concern to me, each of them grand challenges. The fifth topic, **open science**, will be dealt with in a session tomorrow evening.

- Three are grand challenges in science itself, which all academies (and funders and research institutions and journals) will be alert to and maybe need to be more so:
- **Collaboration**,
- **Integrity** – both technical and ethical – and
- **Multidisciplinarity**.
- Without getting these right, science's ability to fulfil its potential within Grand Challenges Facing Humanity, and be trusted in doing so, will be undermined.
- The fourth grand challenge is indeed a Grand Challenge facing Humanity within non-communicable diseases: the burden of **Mental Ill-health**. I will address this in terms of specific global research challenges.

The rise of research networks

Jonathan Adams *Nature* **490** 335 2012 (18 October)

Collaborations between 2005 and 2009 – Elsevier author analysis



The rise of research networks

Jonathan Adams *Nature* **490** 335 2012 (18 October)

- India has a growing research network with Japan, South Korea and Taiwan, although it is not as frequent a collaborator with China as one might expect.
- In the Middle East, Egypt and Saudi Arabia have a strong research partnership that is drawing in neighbours including Tunisia and Algeria. The annual tally of joint Egyptian–Saudi Arabian papers has risen tenfold in the past decade and is accelerating. Less than 5% of these papers have a co-author from the United States, the biggest partner outside the region for both countries.
- Latin America has an emerging research network focused around Brazil, which — despite language differences — has doubled its collaboration with Argentina, Chile and Mexico in the past five years.
- By contrast, Africa has three distinct networks: in southern Africa, in French-speaking countries in West Africa and in English-speaking nations in East Africa.
- These clusters indicate that proximity is just one of several factors in networks. Nigeria, for example, collaborates not with its neighbours in West Africa but with co-linguists in East Africa. This mirrors a global tendency to use paths of least resistance to partnership, rather than routes that might provide other strategic gains.

Integrity: ethical

- There has been much discussion about ethical integrity. Notable amongst the issues of concern is the responsibility of co-authors of research papers, especially in international collaborations.

Technical integrity: irreproducibility

Manifestations:

- Growth in formal corrections in journals
- Failures to replicate high-impact by biotech and pharma
- Public discussions eg in *Nature*, in US Congress
- Discussion so far focused on preclinical laboratory biology, but similar concerns eg in Earth and environmental sciences and materials research.

“A call for transparent reporting to optimize the predictive value of preclinical research”

- **Randomization**
 - Animals should be assigned randomly to the various experimental groups, and the method of randomization reported.
 - Data should be collected and processed randomly or appropriately blocked.
- **Blinding**
 - Allocation concealment: the investigator should be unaware of the group to which the next animal taken from a cage will be allocated.
 - Blinded conduct of the experiment: animal caretakers and investigators conducting the experiments should be blinded to the allocation sequence.
 - Blinded assessment of outcome: investigators assessing, measuring or quantifying experimental outcomes should be blinded to the intervention.
- **Sample-size estimation**
 - An appropriate sample size should be computed when the study is being designed and the statistical method of computation reported.
 - Statistical methods that take into account multiple evaluations of the data should be used when an interim evaluation is carried out.
- **Data handling**
 - Rules for stopping data collection should be defined in advance.
 - Criteria for inclusion and exclusion of data should be established prospectively.
 - How outliers will be defined and handled should be decided when the experiment is being designed, and any data removed before analysis should be reported.
 - The primary end point should be prospectively selected. If multiple end points are to be assessed, then appropriate statistical corrections should be applied.
 - Investigators should report on data missing because of attrition or exclusion.
 - Pseudo replicate issues need to be considered during study design and analysis.
 - Investigators should report how often a particular experiment was performed and whether results were substantiated by repetition under a range of conditions.

Landis *et al.*, *Nature* **490** 187–191 (11 October 2012) doi:10.1038/nature11556

Actions

Nature and Nature research journals have:

- published articles to raise awareness and clarify the issues,
- strengthened our checklist for editors, authors and referees,
- Appointed advisers in basic statistics,
- catalyzed high-level discussions between journal editors, funders and researchers

NIH and Cancer Research UK are among other organisations strengthening their approaches to technical integrity

Technical integrity: generic issues

- Publication of refutations – where?
- Inadequate lab training
- Inadequate lab supervision
- Inadequate data deposition
- “It pays to be sloppy”
- Excessive pressure to publish

Multi-disciplinarity challenges: research assessment

Editorial and peer-review assessment challenges that affect funding agencies too:

- *finding appropriate referees across all relevant disciplines and integrating their assessments*
- *thinking imaginatively and holistically about potential interest in a submission or proposal*
- *understanding alien concepts and language*
- *independent overview and strong judgement*

Climate change challenges

- ***Climate Change, Agriculture and Food Security in Tanzania***
- by Arndt, C., W. Farmer, K. Strzepek and J. Thurlow
[Review of Development Economics](#), 16(3): 378–393, 2012
- Due to their reliance on rain-fed agriculture, both as a source of income and consumption, many low-income countries are considered to be the most vulnerable to climate change.
- **Here, we estimate the impact of climate change on food security in Tanzania. Representative climate projections are used in calibrated crop models to predict crop yield changes for 110 districts in Tanzania. These results are in turn imposed on a highly disaggregated, recursive dynamic economy-wide model of Tanzania.**
- We find that, relative to a no-climate-change baseline and considering domestic agricultural production as the channel of impact, food security in Tanzania appears likely to deteriorate as a consequence of climate change.
- **The analysis points to a high degree of diversity of outcomes (including some favorable outcomes) across climate scenarios, sectors, and regions. Noteworthy differences in impacts across households are also present both by region and by income category.**

Emerging migration flows in a changing climate in dryland Africa

Nature Climate Change 2012

Fears of the movement of large numbers of people as a result of changes in the environment were first voiced in the 1980s. Nearly thirty years later the numbers likely to migrate as a result of the impacts of climate change are still, at best, guesswork.

Owing to the high prevalence of rainfed agriculture, many livelihoods in sub-Saharan African drylands are particularly vulnerable to changes in climate. One commonly adopted response strategy used by populations to deal with the resulting livelihood stress is migration.

Here, we use an agent-based model developed around the theory of planned behaviour to explore how climate and demographic change, defined by the ENSEMBLES project and the United Nations Statistics Division of the Department of Economic and Social Affairs, combine to influence migration within and from Burkina Faso.

The emergent migration patterns modelled support framing the nexus of climate change and migration as a complex adaptive system. Using this conceptual framework, we show that the extent of climate-change-related migration is likely to be highly nonlinear and the extent of this nonlinearity is dependent on population growth; therefore supporting migration policy interventions based on both demographic and climate change adaptation.

Psychiatric disorders

- Neuroscientists can study the genome and genetics, the environmental influences on gene expression, and the neural circuits
- Psychologists can study the behaviours and thought patterns
- Social scientists can study sufferers' view of themselves, and the cultural and social influences.
- Challenge to bring these together, eg in ADHD, eg in childhood stress, eg in adolescents, eg in migrating populations,

General conclusions for editors, funders and academies

- Increasingly, we/you need to be joined up across the disciplines!
- Sounds simple, but isn't.

nature

Vol 463 | Issue no. 7277 | 7 January 2010

www.nature.com/nature

A decade for psychiatric disorders

There are many ways in which the understanding and treatment of conditions such as schizophrenia are ripe for a revolution.

A media circus surrounded President Bill Clinton's visit to a New York medical centre in 2004 for a quadruple heart bypass. Yet barely a whisper was heard about other high-profile individuals' visits there for the treatment of psychiatric disorders.

In Britain, the public donates £500 million (US\$800 million) each year to charities for cancer research. For mental-health research, the figure is a few million, and most of that is for work on neurodegenerative diseases such as Alzheimer's, rather than for earlier-onset conditions that can undermine people's entire lives, such as depressive disorders.

It is time for such disparities to be addressed in a more coherent and aggressive way than in the past. The stigma of psychiatric disorders is misplaced, their burdens on society are significantly greater than more publicized diseases in developed and developing nations alike, and biomedical science is poised to make significant strides. The

characterized, they could lead to a number of alternative conditions. Here, above all, is where progress is needed in the form of reliable biomarkers to identify those at risk and to allow biomedical or cognitive interventions to prevent or mitigate the development of the disorders. Early intervention would lead to better outcomes.

A deeper understanding of the underlying biology is essential to improve diagnoses and therapies. New techniques — genome-wide association studies, imaging and the optical manipulation of neural circuits — are ushering in an era in which the neural circuitry underlying cognitive dysfunctions, for example, will be delineated. Tantalizingly, work in genetics is indicating how non-specific some genes are for schizophrenia, having

“Early detection and a clearer understanding of environmental factors may allow prevention of psychiatric disorders.”

Global burdens of disease

WHO 2004

The screenshot shows a Windows Internet Explorer browser window displaying a WHO report on global burdens of disease. The address bar shows the URL: http://www.who.int/healthinfo/global_burden_disease/GBD_report_2004update_part4.pdf. The page content includes a table of the top 20 diseases by DALYs and a sidebar with navigation links.

Disease or injury	DALYs (millions)	Per cent of total DALYs
1 Lower respiratory infections	94.5	6.2
2 Diarrhoeal diseases	72.8	4.8
3 Unipolar depressive disorders	65.5	4.3
4 Ischaemic heart disease	62.6	4.1
5 HIV/AIDS	58.5	3.8
6 Cerebrovascular disease	46.6	3.1
7 Prematurity and low birth weight	44.3	2.9
8 Birth asphyxia and birth trauma	41.7	2.7
9 Road traffic accidents	41.2	2.7
10 Neonatal infections and other ^a	40.4	2.7
11 Tuberculosis	34.2	2.2
12 Malaria	34.0	2.2
13 COPD	30.2	2.0
14 Refractive errors	27.7	1.8
15 Hearing loss, adult onset	27.4	1.8
16 Congenital anomalies	25.3	1.7
17 Alcohol use disorders	23.7	1.6
18 Violence	21.7	1.4
19 Diabetes mellitus	19.7	1.3
20 Self-inflicted injuries	19.6	1.3

Unipolar depression makes a large contribution to the burden of disease, being at third place worldwide and eighth place in low-income countries, but at first place in middle- and high-income countries. Effective treatments for depression are available, suggesting that this burden could be reduced.

Cigarette smoking is a major and entirely preventable cause of burden of disease in middle- and high-income countries. Chronic obstructive pulmonary disease is in fifth place in middle-income countries and seventh place in high-income countries, and lung cancer is in ninth place in high-income countries. Cigarette smoking also contributes to the burden of disease from ischaemic heart disease and cerebrovascular disease, and affects communities in low-income countries as well. Alcohol use disorders are another important preventable contributor to burden of disease in middle- and high-income countries.

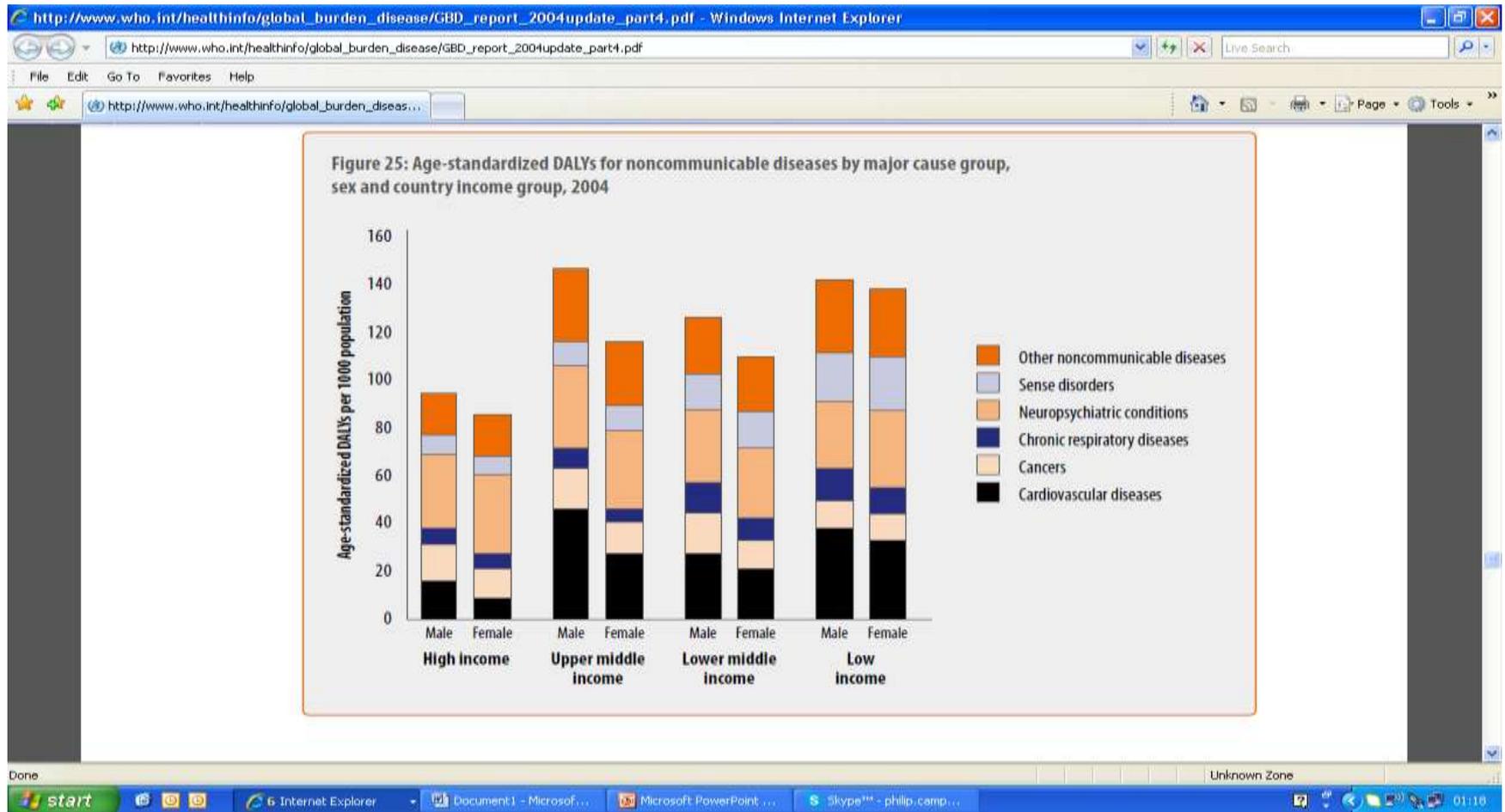
Considerable variation between regions in the burden of disease

The WHO regions fall into two groups – those in which the burden of disease is dominated by infec-

2
3
4
Annex A
Annex B
Annex C
References

Global burdens of disease

WHO 2004



Mental disorders: frequently early onset



Neurological disorder: frequently later onset

birth

Old age

Mental Disorders with proportionally high incidence in

Childhood/adolescence

Mental retardation
Hyperkinetic dis./ADHD
Conduct disorders
Pervasive developm.dis.
Phobias
Anorexia nervosa
Some epilepsies

Late adolescence

Drug use disorders
Panic, OCD, PTSD
Mood disorders
Somatoform disorders
Schizophrenic dis.
Bulimia nervosa
Personality disorders.

Adulthood (ages 20-50)

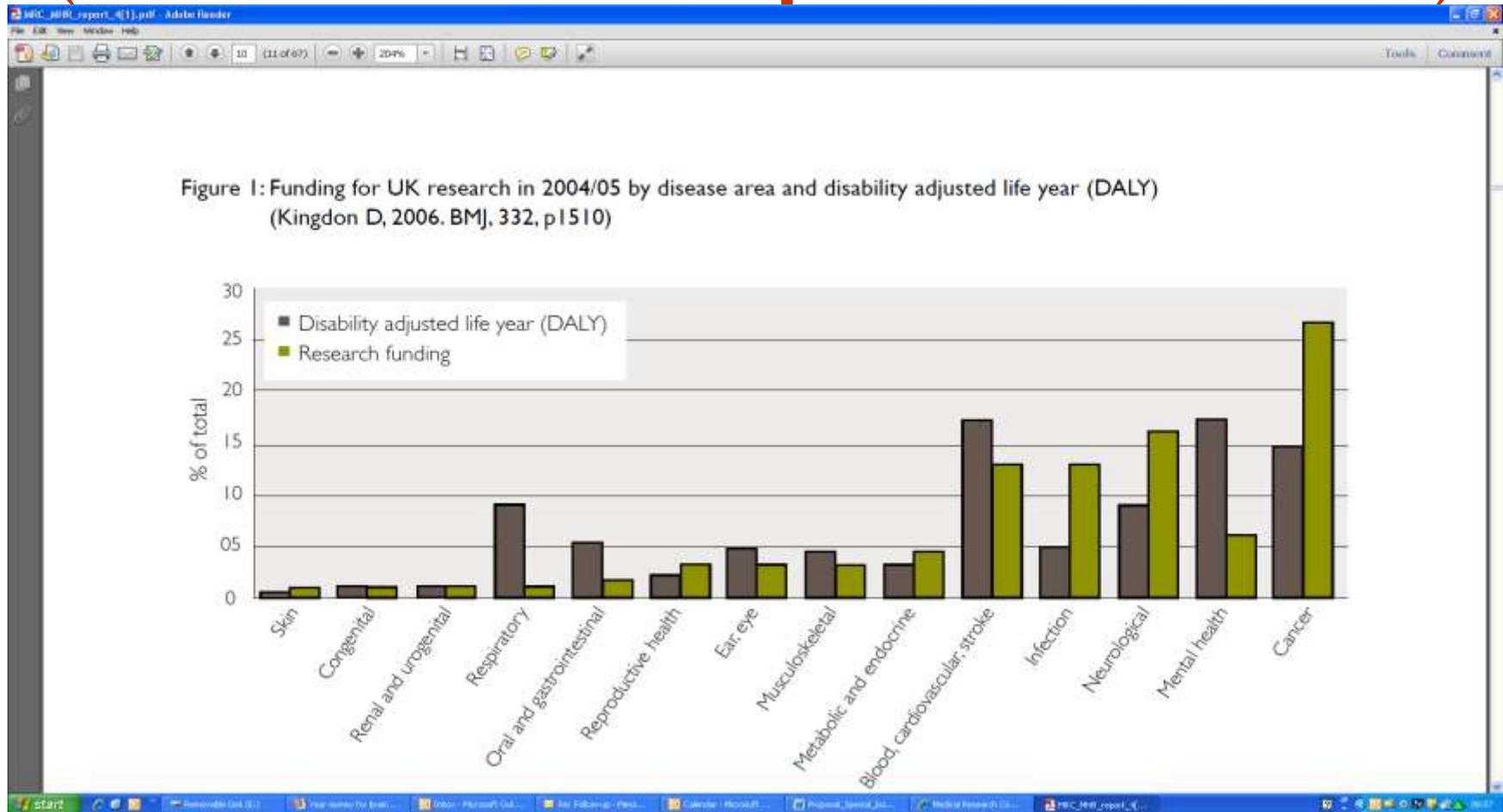
Alcohol dependence
Depression
Generalized Anxiety dis.
Sleep disorders
Multiple Sclerosis
Traumatic brain injury
Brain tumours
Neuromuscular dis.

Later life

Stroke
Parkinson's disease
Dementias
Sleep disorders
Subthreshold anxiety
and depression
„multimorbidity“

Contrast between health burdens and research effort – UK

(Other national comparisons welcome!)



Examples of research

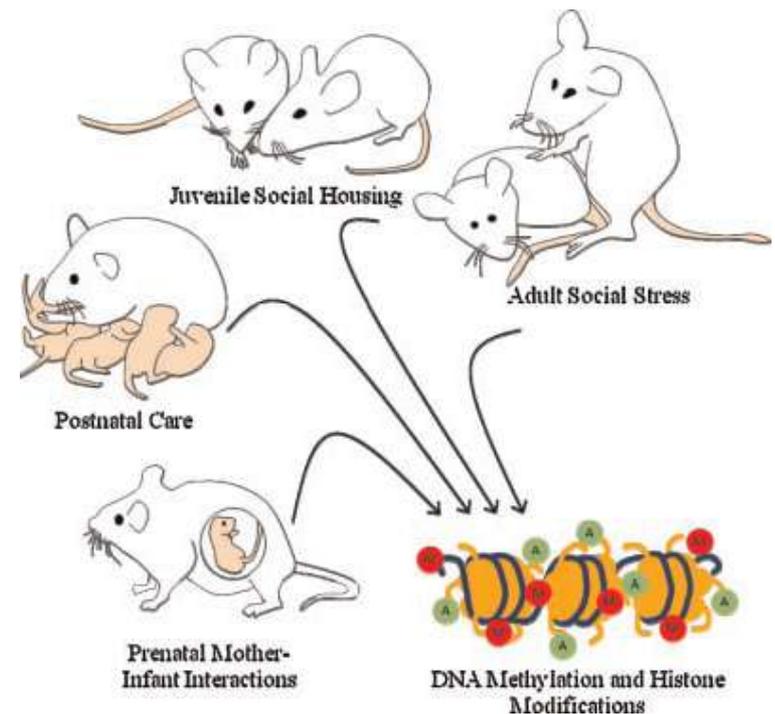
- New biological tools
- Genetics
- Environment
- Social science
- Psychological treatments

Biology of environmental influences

Epigenetic consequences of social experiences across the lifespan.

Emerging evidence suggests that prenatal environmental exposures, postnatal mother–infant interactions, juvenile social rearing, and adult social stress can alter epigenetic processes such as DNA methylation (red circles) and histone acetylation (green circles)/methylation with long term consequences for gene expression, physiology, and behavior.

(Ack. F A Champagne 2010)

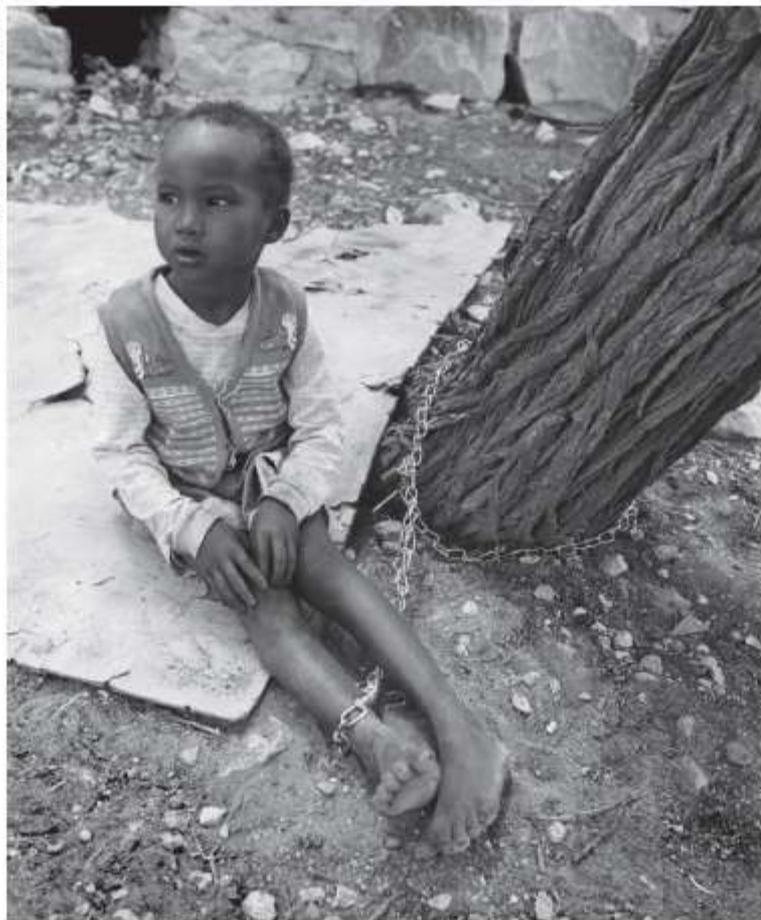


Alternative therapeutic strategies to address cognitive impairment

Therapeutic approach	Influence on emotional symptoms*	Influence on cognitive impairment*	Psychiatric disorders targeted
Currently available pharmacotherapy	+	-/0/+	Schizophrenia, depression, bipolar disorder, anxiety disorders
Deep-brain stimulation or electroconvulsive therapy	+	0/-	Major depression
Repetitive transcranial magnetic stimulation	0/+	0/+	Mainly depression (autism, schizophrenia)
Cognitive behavioural therapy	+	0	Mainly depression (anxiety disorders)
Cognitive remediation therapy	0/+	+	Mainly schizophrenia (depression)
Exposure therapy for desensitization	0/+	+	Post-traumatic stress disorder, obsessive compulsive disorder, phobias, social anxiety disorders
Improved drugs (alone and in combination with above strategies)	+	+	Dependent on mechanism of action

*The '+' symbol corresponds to improvement; the '-' symbol corresponds to worsening; and '0' corresponds to no marked change.

H. TIMMERMAN/GEORGIA INSTITUTE OF TECHNOLOGY



Improving treatment for children with mental illness, like this girl in Somalia, is an urgent priority.

Grand challenges in global mental health

A consortium of researchers, advocates and clinicians announces here research priorities for improving the lives of people with mental illness around the world, and calls for urgent action and investment.

Schizophrenia, depression, epilepsy, dementia, alcohol dependence and other mental, neurological and substance-use (MNS) disorders constitute 13% of the global burden of disease (Table 1), surpassing both cardiovascular disease and cancer¹. Depression is the third leading contributor to the global disease burden, and alcohol and illicit drug use account for more than 5% (ref. 2). Every seven seconds, someone develops dementia³, costing the world up to US\$609 billion in 2009 (ref. 4). By 2020, an estimated 1.5 million people will die each year by suicide, and between 15 and 30 million will make the attempt⁵.

The absence of cures, and the dearth of preventive interventions for MNS disorders, in part reflects a limited understanding of the brain and its molecular and cellular mechanisms. Where there are effective treatments, they are frequently not available to those in greatest need. In 83% of low-income countries, there are no anti-Parkinsonian treatments in primary care; in 25% there are no anti-epileptic drugs⁶. Unequal distribution of human resources — between and within countries — further weakens access: the World Health Organization's European region has 200 times as many psychiatrists as in Africa⁷. Across all countries, investment in fundamental research into preventing and treating MNS disorders is disproportionately low relative to the disease burden⁸.

To address this state of affairs, the Grand Challenges in Global Mental Health initiative has identified priorities for research in the next 10 years that will make an impact on the lives of people living with MNS disorders. The study was funded by the US National Institute of Mental Health (NIMH) in Bethesda, Maryland, supported by the Global Alliance for Chronic Diseases (GACD), headquartered in London. Answers to the questions posed will require a surge in discovery and delivery science. We use the term 'mental health' as a convenient label for MNS disorders. We exclude conditions with a vascular or infectious aetiology (such as stroke or cerebral malaria), because these fell within the scope of the two previous grand challenges initiatives — in global health and in chronic non-communicable diseases⁹.

This initiative differs from previous priority-setting exercises for mental ▶

TABLE 2 | GRAND CHALLENGES FOR MNS DISORDERS

	Top 25 challenges*	Illustrative research questions
Goal A Identify root causes, risk and protective factors	<ul style="list-style-type: none"> Identify modifiable social and biological risk factors across the life course Understand the impact of poverty, violence, war, migration and disaster Identify biomarkers 	<ul style="list-style-type: none"> What is the relationship between early fetal and child development and the onset of MNS disorders? What are the phenotypes and endophenotypes of MNS disorders across cultural settings? What gene-environment interactions are associated with the increased risk for mental disorders? What factors promote resilience and prevent mental disorders in persons at extreme social disadvantage? What role does social context play in the persistence of MNS disorders throughout life?
Goal B Advance prevention and implementation of early interventions	<ul style="list-style-type: none"> Support community environments that promote physical and mental well-being throughout life Reduce the duration of untreated illness by developing culturally-sensitive early interventions across settings Develop interventions to reduce the long-term negative impact of low childhood socioeconomic status on cognitive ability and mental health Develop an evidence-based set of primary prevention interventions for a range of MNS disorders Develop locally appropriate strategies to eliminate childhood abuse and enhance child protection 	<ul style="list-style-type: none"> Which behavioral skills can enhance executive function, resilience and cognitive flexibility throughout life? What neuroprotective agents and/or cognitive retraining paradigms can be used during the period of rapid brain development to reduce vulnerability to disorders in adolescence? How effective are home- and school-based interventions for child abuse and neglect?
Goal C Improve treatments and expand access to care	<ul style="list-style-type: none"> Integrate screening and core packages of services into routine primary health care Reduce the cost and improve the supply of effective medications Develop effective treatments for use by non-specialists, including lay health workers with minimal training Incorporate functional impairment and disability into assessment Provide effective and affordable community-based care and rehabilitation Improve children's access to evidence-based care by trained health providers in low- and middle-income countries Develop mobile and IT technologies (such as telemedicine) to increase access to evidence-based care 	<ul style="list-style-type: none"> How effective are brief screening tools for the detection of MNS disorders in routine care settings? How effective are interventions for serious mental disorders delivered by lay health workers? How will increased understanding of neural circuits lead to alternatives to current pharmacological interventions? How can mobile-phone technology be used to monitor seizure frequency? How can video games and other electronic media be used for cognitive remediation across cultural settings? What psychosocial interventions produce the best outcomes for community-based care for MNS disorders across cultural settings?
Goal D Raise awareness of the global burden	<ul style="list-style-type: none"> Develop culturally informed methods to eliminate the stigma, discrimination and social exclusion of patients and families across cultural settings Establish cross-national evidence on the cultural, socioeconomic and services factors underlying disparities in incidence, diagnosis, treatment and outcomes Develop valid and reliable definitions, models and measurement tools for quantitative assessment at the individual and population levels for use across cultures and settings Establish shared, standardized global data systems for collecting surveillance data on the prevalence, treatment patterns and availability of human resources and services 	<ul style="list-style-type: none"> What are the components of effective interventions to reduce stigma associated with MNS disorders? What interventions to reduce stigma and discrimination can be targeted to and implemented in health and social service settings in different health-system environments? What is the impact of macroeconomic factors (such as unemployment rates, international trade, national income) on the prevalence of MNS disorders over time? What is the impact of policy initiatives on the coverage of treatment for MNS disorders? What measurement factors contribute to differences in the prevalence of mental disorders across ethnic groups within and between countries?
Goal E Build human resource capacity	<ul style="list-style-type: none"> Increase capacity in low- and middle-income countries by creating regional centers for mental-health research, education, training and practice that incorporate the views and needs of local people Develop sustainable models to train and increase the number of culturally and ethnically diverse lay and specialist providers to deliver evidence-based services Strengthen the mental-health component in the training of all health-care personnel 	<ul style="list-style-type: none"> What is the most effective way to train primary health-care workers to deliver evidence-based care with adequate fidelity to guidelines? What is the comparative effectiveness of care for MNS disorders by different cadres of health-care providers? What are the views of low-income communities in high- and low-income countries on the priority research questions for MNS disorders?
Goal F Transform health-system and policy responses	<ul style="list-style-type: none"> Establish and implement minimum health-care standards for MNS disorders around the world Redesign health systems to integrate MNS disorders with other chronic-disease care, and create parity between mental and physical illness in investment into research, training, treatment and prevention Incorporate a mental-health component into international aid and development programmes 	<ul style="list-style-type: none"> What can we learn from different approaches (and associated costs) to integrated delivery of care across health systems? What are the most effective health-system-wide strategies to reduce consumption of alcohol and illicit drugs? What is the impact of legislation that ensures parity between mental and other illnesses on access to mental-health services?
Summary principles	<ul style="list-style-type: none"> Use a life-course approach to study Use system-wide approaches to address suffering 	<ul style="list-style-type: none"> Use evidence-based interventions Understand environmental influences

*The order in which the challenges are presented does not indicate frequency of endorsement or relative importance. **Bold type** denotes the top five challenges ranked by disease-burden reduction, impact on equity, immediacy of impact and feasibility.

Grand Challenge includes:

- Goal: Identify root causes, risk and protective factors
- One of top 25 challenges: understand the impact of poverty
- One research question: understand relationship between early fetal and child development on onset of mental health disorders (which requires multidisciplinary approach)

Academies roles include fostering:

- In the context of poverty and sustainable development, academies need to foster:
- Within research and research policy, strategic collaborations, ethical and technical integrity in science, multidisciplinary integration;
- As a research goal in global health, support for prevention and mitigation of mental ill-health

**Thanks for your
attention!**

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