Editorial

Neuroimaging and global health

This special issue is motivated by an essential paradox of contemporary Brain Mapping.

On the one hand, there is unprecedented funding for national and international brain initiatives. New technologies, discoveries about brain mechanisms, and elucidation of physiopathology overwhelm our possibilities to interpret them. Research is accelerated via common IT infrastructures, harmonized practices, and unified acquisition protocols. These tremendous international efforts generate hope towards substantial reductions in the Global Burden of Brain Disorders might result.

On the other hand, the vast majority of people in the world are not benefitting, nor will benefit in the near future from current neuroscience and technological breakthroughs. This was the consensus of a group that met in the World Health Organization (WHO) headquarters in June 2016 consisting of representatives of the US BRAIN project, the European Human Brain Project, the Japan Brain/MINDS, and the Chinese, Australian, and Cuban Brain Projects.

The cause of this mismatch between brain research efforts and their impact on global health discussed with the conclusion that the cause is multifactorial.

- The primary efforts of the international brain initiatives are concentrated in high development countries, where brain research can benefit from expensive and sophisticated tools.
- There is an insufficient linkage between brain research and public health needs, including delivery within primary health care (even in wealthy countries).
- Researchers in Low and Middle-Income Countries(LMIC) are marginalized due to economic inequity that lead to a lack of adequate research tools.

To discuss how neuroscientists could contribute to solving these issues, the 2016 meeting was organized around four topics of interest: 1) prevention and reduction of the risk for brain disorders in developing countries, 2) neurodiagnostic, neuroinformatics/telemedicine and treatment, early detection, and stratification of subjects at risk, 3) the effective treatment of mental diseases, 4) the development of screening devices for large populations to increase the awareness of the burden of mental health in developing countries.

These issues have remained a continuing concern for the Organization of Human Brain mapping (OHBM), and at one of its Council meetings, Michael Breakspear, Editor-in-chief of NEUROIMAGE, launched the initiative to dedicate a special issue to promote further discussion of these topics. OHBM also facilitated the creation of regional chapters to promote neuroimaging research in areas where less resources are either available or devoted to research, example the chapter for Latin America LABMAN. This special issue- Neuroimaging and Global Health, has now concluded with the publication of a carefully curated collection of articles that respond to the challenges in this area of research.

This special issue provides an overview of worldwide Neuroimaging research, highlighting cutting-edge research within the context of global health. Special care was taken to have papers from all economic settings. It showcases work from LMIC and reveals how valuable such work can be despite inequity, the brain drain, and lack of equipment and funding. It also brings to the forefront the effects on the brain of adversities resulting from poverty, violence, and parental neglect manifested in inflammation, stunting, and malnutrition, provoking retardation in brain maturation, increased neuropathology, and premature brain aging.

In this issue, we present 16 papers, 11 original research (10 cross-sectional and one longitudinal), 2 reviews and 1 proof of concept of a new technology. In addition, there are two papers on ethics. The authors are from 24 countries that include five continents.

The central tendency observed in the research papers is the international collaboration, with bi-national being the most frequent ($n = 7$ papers), between one high-income country and the other LMIC. For example, Ireland-Turkey, or USA researchers with colleagues in Bangladesh, Brazil, Nigeria, Colombia, or Gambia-UK. Or three partners: South Africa, the USA, and the UK.

The datasets reported clinical populations in pediatrics, lifespan cohorts, Alzheimer's Disease, and stroke, collected from 20 different countries. America; Argentina, Barbados, Brazil, Chile, Colombia, Cuba, and United States. Europe: Germany, Poland, Russia, Switzerland, Turkey. Africa: Gambia, Ghana, Nigeria, South Africa, Asia: Bangladesh, China, Malaysia, and Australia.

The technologies employed were: CT, MRI, fNIRS, EEG-ERPs, including modern technologies like portable MRI and fNIRS, and different experimental designs and analysis, machine learning, VBM SPM, EEG topographic, and tomographic EEG source analysis.

1. Pediatrics and neurodevelopment

The research presented here covering topics related to neurodevelopment was performed in countries with a high burden of infectious diseases and psychosocial stressors representative of many LMICs countries (Gambia, South Africa, Colombia, Mexico, Bangladesh). Infants and children in low- and middle-income countries are frequently exposed to adversity-related risk factors (poverty, inflammation, inflammation, stunting, malnutrition), inducing retardation in brain maturation and poor neurodevelopmental outcomes. There is a need for objective markers, which can be used for early identification and intervention during a critical time of neurodevelopment. Under well-established or carefully designed paradigms, ERPs can be potential electrophysiological markers

to inform our understanding of the neural correlates and neurodevelopmental sequela of early adversity.

One of the results from Bangladesh showed how the neural circuitries associated with social attention and recognition memory of faces might be potential pathways by which inflammation affects cognitive development (Xie et al., 2019 in this issue) using a face-oddball paradigm.

Auditory event-related potentials (ERP) discriminate habituation and novelty detection in infants between 1 and 5 months living in the United Kingdom and Gambia, West Africa (Katus et al., 2020). The Gambian cohort didn't present the expected change of intensity to a novelty-based response.

A South Africa team (Wedderburn et al., 2020) studied children 2–3 years old and found that cortical surface area and thickness within temporal and frontal regions were associated with cognitive impairment with respect to language development.

In an extremely impoverished urban setting of Dhaka, Bangladesh (Turesky et al., 2020), the relationship between anthropometric indicators (stunting, underweight, and wasting) and brain structural measures were tested for the first time. Positive semi-partial correlations were observed between white matter volume and height and weight measures.

To study a cohort of 30 malnourished children in Colombia, Fishell et al. (2020) introduced, a portable functional near-infrared spectroscopy (fNIRS) with evoked potentials to the "passive word listening task" replicating previously published work.

A comprehensive longitudinal interventional study in Mexico is reported by (Harmony, 2021) with 445 children with prenatal and perinatal risk of brain damage, with more than 80% having abnormal MRI scans. After 8 years of follow-up with Katona's neurohabilitation method, 78% of highly preterm, 76% very preterm, and 78% late preterm, respectively, showed typical neurodevelopment. This work highlights the need to evaluate, at an early age, all newborns with prenatal and perinatal risk factors for brain damage. The paper also describes a neuroimaging facility in an LMIC that has achieved excellence and linked its efforts to solve health issues of the local underserved population.

Childhood malnutrition and the study of its impact on neurodevelopment were summarized by Galler et al. (2021). It highlighted how most studies have relied on neuropsychological tests, school performance, and mental health and behavioral measures. Few studies, in contrast, have assessed brain structure and function, and to date, these have mainly relied on low-cost techniques, including electroencephalography (EEG) and the application of evoked potentials (ERP). The use of more advanced neuroimaging methods, including magnetic resonance imaging (MRI) and functional near-infrared spectroscopy (fNIRS), has been limited by cost factors and the lack of availability of these technologies in developing countries where malnutrition is nearly ubiquitous.

The critical and neglected topic of victims of urban violence in Brazil at risk of developing Posttraumatic Stress Disorder (PTSD) is addressed by (Lobo et al., 2021). They aimed to investigate how the severity of posttraumatic stress symptoms (PTSS) is related to motor preparation against visual threat cues. Longer ERPs latencies and a slower reaction time indicate the severity of PTSD.

2. Aging and dementia

A multi-center and multinational study, including Argentina, Chile, Australia, Poland, and Colombia, validated a benchmark for future assessments of reliability and reproducibility in Alzheimer's Disease (AD) using machine-learning tools to integrate multimodal EEG and MRI measures (Bachli et al., 2020). Executive functions and brain atrophy volume (voxel-based morphometry from frontotemporal-insular and temporoparietal regions) identified the most relevant features in predicting the incidence of AD.

The first direct comparison of EEG and structural MRI (sMRI) for the classification of AD and amnestic MCI (aMCI) is reported in Turkey by (Farina et al., 2020). They found that sMRI outperformed resting-state EEG in classifying AD (AUCs= 1.00 vs. 0.76, respectively). However, EEG and sMRI were only moderately effective at distinguishing aMCI from healthy aging (AUCs= 0.67–0.73). The addition of EEG in the prediction equation didn't add a benefit relative to Mini-Mental State Examination (MMSE) scores alone.

Another contribution from Ghana and Nigeria (J. Li et al., 2020) is related to the Stroke Investigative Research and Educational Network, the largest study of stroke patients in Africa, with MRI data for each patient to confirm stroke. Associations between white matter hyperintensities and age and waist/hip ratio previously identified in Western countries were demonstrated for the first time in a resource-limited, homogeneous black African community using low-field MR scanners.

3. Methodological and international collaboration

One of the best examples of international collaboration is the multinational EEG norms based on quantitative EEG (qEEG) analysis, using cross-spectrum datasets from 9 countries China, Malaysia, Germany, Switzerland, Russia, Barbados, Cuba, Colombia, and United States, providing more than 1500 EEGs from 5 yr to 97 yr. To weed out non-biological factors, they proposed a simple but efficient harmonization method based on normative samples, which is a refined and fast algorithm to eliminate biological covariates from "nuisance effects" (Li et al., 2022). Here the novelty consisted in the methodological approach using harmonization between datasets and the Riemannian geometry and Hermitian vectorization of the cross-spectra data. This work builds upon the long tradition of quantitive EEG, introduced into the health system by the Cuban Neuroscience Center (Valdes et al., 1992; John et al., 1977).

Another example of international cooperation is the longitudinal EEG study of 40 years of long-term effects of malnutrition in the cohort of Barbados with authors from Cuba, the USA, China, Canada, Switzerland, Pakistan, and Barbados. This malnutrition study employed EEG source analysis (Bosch-Bayard et al., 2022). This unique longitudinal study demonstrates the consequences of malnutrition on the brain.

Ethics. It's important to mention that discussion on research ethics often focusses on the issue of performing studies in developing countries and not on "the ethics of not performing studies in developing countries".

This topic is addressed by (Shen et al., 2021), who highlight the need for "field-based neuroimaging research in (LMICs) to improve local capacity to conduct structural and functional neuroscience studies". Facilitating MRI research in remote settings can also diversify reference databases in neuroscience, improve understanding of brain development and degeneration across the lifespan in diverse populations, and help to create reliable measurements of infant and child development. Still, there are few studies addressing the ethical, legal, and social issues (ELSI) related to neuroscience research in LMICs. To address this gap, Shen et al. (2021) presents findings from the first phase of an envisioned multi-staged and iterative approach for creating ethical and legal guidance in a complex global landscape. The authors argue that a guiding principle for field-based MRI research in these contexts should include local communities and research participants throughout the research process to create sustained local value.

In addition to neuroimaging, genetics is a rapidly developing field that combines neuropsychiatric genetics studies with imaging modalities to investigate how genetic variation influences brain structure and function (Palk et al., 2020). While neuroimaging genetics studies offer several scientific advantages, they also include challenges. Global neuroimaging genetics collaborations have been created to pool and compare brain data and replicate study findings in response to these challenges. Only recently has ttention been paid to inequity, exploitation, and data sharing risks. Moreover, neuroimaging genetics research in low- and middle-income countries must address the issue of feedback on findings and the risk of stigmatizing interpretations of mental disorders.

Drawing on insights from sociology, anthropology, and the history of science and medicine, (Pickersgill, 2021) considers some of the social dimensions and implications for neuroimaging research undertaken within (LMICs). The author argues that the use of neuroimaging technologies in population research has the potential to contribute to solidifying –or even introducing –a biological (and specifically brain-based) understanding of mental ill-health within the communities under study. The social dimensions and implications of neuroimaging are issues that all researchers using these technologies need to anticipate and explicitly plan for (and potentially seek to mitigate). Without adequate consideration, neuroimaging research carries particular risks in extending the epistemological coloniality associated with high income countries (HIC) sponsored studies conducted within LMIC settings.

Finally, we should mention recent efforts to galvanize, organize and provide IT infrastructure for international brain health. The Global Brain Consortium (GBC) was created in 2019 to focus on human imaging, initially selected EEG for its advantages (cheaper, portable, non-invasive), genomics, and behavioral data to accelerate our understanding of the spatiotemporal dynamics of brain states, e.g., neurodevelopment, neuroplasticity, and disease progression. The GBC will promote global precision brain health research with and for disadvantaged populations worldwide, including LMIC, to make a difference where the burden of mental disorders is highest but lacks access to expensive imaging technologies Global Brain Consortium Homepage.

4. Points to consider for more discussion

Inclusion and diversity of authors. This special issue has contributed significantly to increasing the diversity, with authors from 5 continents: Australia, Asia, Africa, Europe, and Latin America, with 10 women as first authorship and more than 50% women among all co-authors. Note that authors include people with diverse socio-cultural, economic, and ethnic backgrounds.

Diversity data collection. The datasets studied here were also very diverse, collected in 21 countries, 12 in LMICs: Argentina, Brazil, Colombia, Cuba, Mexico, Turkey, Gambia, Ghana, Nigeria, South Africa, Bangladesh, and Malaysia, published for the first time. The nine datasets belonged to countries classified in the Middle-High income list: Chile, Barbados, Poland, United States, Switzerland, Germany, Australia, Russia, and China.

While over 7 billion people live on our axial precessing planet, most neuroimaging studies occur in higher-income countries. In fact, in this special issue, 11 of the 20 datasets published are collected in low-middle income countries, representing a step in the direction of diversity in neuroimaging research.

5. Direction for improvement

a) There is an increasing tendency to do neuroimaging research in LMICs, but the results of many of the studies can be considered preliminary because of the small size of the samples, the lack of confounders or enough covariates to explore the influences, among others.

b) Inferences drawn from these findings in LMIC can also be problematic because infants in this low-resource setting are exposed to a myriad of risk factors, each of which may alter brain structure differently and only the most standard covariates were applied in these studies, for example, age, gender, socio-economic status (incomes household), educational level or the parents, for example. Thus, understansinf potential biases is an important challenge in the field. It's challenging to match risk factors to their corresponding effects (a task that would be further complicated by interaction effects arising from multiple risk factors).

c) There are many difficulties of recordings children in obtaining structural neuroimaging techniques of children without sedation, as is the standard practice in clinical settings. This is more complicated in LMIC, where the scanners, EEG, or NIRS equipment are scarce, and the technicians are less prepared. The need to recruit families in person due to limited communication channels; caregivers have less information and can be reluctant to cooperate if the children are not sick.

d) The results of many of the studies can be considered preliminary because of the small size of the samples, the lack of confounders or enough covariates to explore the influences, the lack of ground truth (fNIRS). Studies are predominantly association, not causation studies and uncorrected measures are often used.

But this is understandable because this is the first time that a call for neuroimaging papers from LMICs has been made. Even if the results are promising, it is unclear how this research would translate to most of the population at risk living in developing countries,because not always the methodologies are relevant to unveiling the neural mechanisms underlying the cognitive deficits identified in populations at risk in underdeveloped countries. Ignoring the challenges of research in low-income countries only perpetuates inequity has been recently highlighted by a special number of Nature (Editorial, 2022; Ferreira, 2022; Jambo, 2022; Sidik, 2022; Tollefson, 2012), especially in post-COVID era.

6. Further steps

1) We need to establish population-based and federated studies, to obtain more reliable results able to be introduced on a large scale with the support of international organizations, research funders and national governments. It's imperative to unify the neuroimaging research efforts geographically and globally and promote actions to impact these majorities' quality of life.

2) There is an urgent need for portable and affordable tools for assessing brain function in low-resource settings such as EEG, low-field fMRI, fNIRS, or others.

These actions are likely to contribute to the implementation of World Health Organzation's Intersectoral Global Action Plan on Epilepsy and other Neurological Disorders, 2022–2031, approved by the World Health Assembly in May 2022. https://www.who.int/news/item/28-04-2022-draft-intersectoral-global-action-plan-on-epilepsy-and-other-neurological-disorders-2022-2031

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