REVIEW ARTICLE

Population neuroscience: challenges and opportunities for psychiatric research in low- and middle-income countries

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Objective: Population neuroscience is an emerging field that combines epidemiology and neuroscience to study how genes and the environment shape typical and atypical brain functioning. The objective of this study was to review key studies on population neuroscience from low- and middle-income countries (LMICs) and to identify potential gaps vis-à-vis studies conducted in high-income countries.
Methods: We conducted a systematic review to search for longitudinal cohort studies investigating the development of psychiatric disorders in children and adolescents in LMICs. We performed an electronic search in the EMBASE and MEDLINE databases from inception to July 5th, 2019.
Results: We found six cohorts from four countries that met our search criteria: three cohorts from Brazil, one from China, one from South Africa, and one from Mauritius. Relevant examples of findings from these studies are reported.
Conclusion: Our results demonstrate the impact of the valuable science output these cohort designs promote, allowing LMICs to have a share in frontline global psychiatry research. National and international funding agencies should invest in LMIC population neuroscience in order to promote replication and generalization of research from high-income countries.

Keywords: Neuroscience; epidemiology; population neuroscience; low- and middle-income countries; review

Introduction

Psychiatry is a hybrid discipline encompassing the study of a variety of behavioral abnormalities, conceptualized both clinically and historically, that ultimately result from qualitative and/or quantitative dysfunctions of the brain. It is strongly pragmatic, having to serve the needs of clinicians, administrators, and funders, but is progressively becoming more scientifically oriented. Two of the major scientific fields that inform psychiatry are epidemiology and neuroscience, which have developed completely separately and, until recently, rarely interacted with each other.

Psychiatric epidemiology has been essential to the development of scientific psychiatry. For example, it has identified the prevalence, recurrence, and chronicity of psychiatric disorders,[1] as well as their developmental nature.[2,3] It has revealed problems with our diagnostic reliability (low agreement between independent opinions of investigators)[4] and raised questions about the validity of psychiatric disorders (low predictive information with respect to class membership). In its application to therapeutics (e.g., randomized clinical trials), it has revealed the non-specificity of our treatment options.[5] In its interaction with genetics, it has exposed the fragilities of our diagnostic boundaries[6] and clarified the complexities of causality of psychiatric traits.[7]

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Population neuroscience is a new subfield that aims to bring together epidemiology and neuroscience to increase the external validity, reliability, and generalizability of neuroscience findings.[8,9] The overwhelming amount of complexity involved in interacting risk factors (genome and environment) and resulting phenotypes at several levels of biological coherence (phenome) is the main rationale for this integration. Scientific integration can help develop methods to deal with complex phenomena, not only as a result of the additive effects of their components, but also to study the characteristics of the phenomena as a whole.[10] According to Paus,[8,9] who coined the term "population neuroscience," the main goals of this new discipline are twofold: a) to advance our understanding of interindividual variability in the human brain and its behavioral products; and b) to use information from genes and environments to individualize prediction of risk in order to develop personalized preventive strategies tailored to the at-risk individual.[8,9]

Here, we review the literature on longitudinal, population-based cohort studies from low- and middle-income countries (LMICs) that utilize genetics or neuroimaging to explore the interindividual brain variability of psychiatric disorders during neurodevelopment and the predictive ability of certain biological and environmental risk factors. This is essential because risk factors are populational, while disease is an individual experience.

Methods

The systematic review followed PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines.

Search strategy

We performed an electronic search in the EMBASE and MEDLINE databases, on July 5th, 2019, using the following keywords (MeSH and text words) to describe 1) study population: children, child, childhood, adolescent, adolescence, teenager, youth; 2) study design: cohort studies; 3) outcomes of interest: psychopathology, psychiatric disorder, mental disorder, psychiatry; 4) developing country, developing world, low and middle income country, LMIC, low income country, middle income country, and the individual country names defined in 2015 by the World Bank lending classification as low or middle income using Gross National Income (GNI) per capita of less than $12,735. We also handsearched the reference lists of the selected papers and of relevant reviews for additional studies.

Inclusion and exclusion criteria

Only original, peer-reviewed articles in English, without restrictions on the date of publication, were included. An article was eligible if it referred to a longitudinal, population-based study design, regardless of recruitment method; was set in a LMIC; included participants from birth to 17 years old; assessed any standardized psychiatric diagnosis on individuals up to 17 years old; and

utilized measurements in genetics, neuroimaging, psychopathology, or cognition. Articles with a cross-sectional design were included if they utilized data from cohort studies that satisfied the inclusion criteria. Studies conducted with samples not representative of the population were excluded, as well as those that recruited subjects with a previous psychiatric diagnosis (e.g., schizophrenia).

Two investigators (AC and ED) screened all studies by title and abstract independently. The studies included for the full-text review phase were also evaluated independently by the two authors. After each phase was completed, blinding was removed and any conflicts were resolved by consensus, consulting with another investigator (JM) when necessary.

Data extraction

Two authors (AC and ED) extracted the following information independently from each included study: metadata (cohort identification, year of beginning, country of origin), characteristics of the participants (number, age), study design, length of the cohort, assessment instruments, and main findings. The main findings were extracted selectively so as to provide some examples of the potential outcomes obtained from cohort studies conducted in LMICs.

Results

Figure 1 provides a PRISMA flow diagram of study screening and inclusion.

Our search resulted in six cohort studies from four countries (Brazil, China, South Africa, and Mauritius), five of which are birth cohorts. Table 1 describes the design, including sample characteristics, as well as examples of findings from each study. The High-Risk Cohort Study for the Development of Childhood Psychiatric Disorders (HRC), an ongoing longitudinal cohort study conducted in Brazil, is highlighted here due to its innovative methodology among LMICs that includes psychopathology, cognitive assessments, genetics, and neuroimaging. Our search elicited 12 studies resulting from the HRC, including the following topics and methodologies: functional connectivity and depression,[11] the role of inflammation in mental health problems in children,[12] cortical structure in children and adolescents with psychiatric disorders,[13] spontaneous brain activity involved in obsessive compulsive symptoms,[14] self-harm,[15] perinatal complications and mental health problems in children and adolescents,[16] dynamic functional connectivity and psychopathology,[17] attention bias to threat,[18] the association between obsessive compulsive symptoms and psychopathology/behavior problems,[19] the genetics of attention-deficit/hyperactivity disorder (ADHD),[20] the utilization of mental health services by children,[21] and the economic impact of childhood mental disorders.[22]

The 1993 and 2004 Pelotas Birth Cohorts have also been conducted in Brazil and produced significant results in child and adolescent mental health. Eight studies from the 1993 Pelotas Birth Cohort were included from our
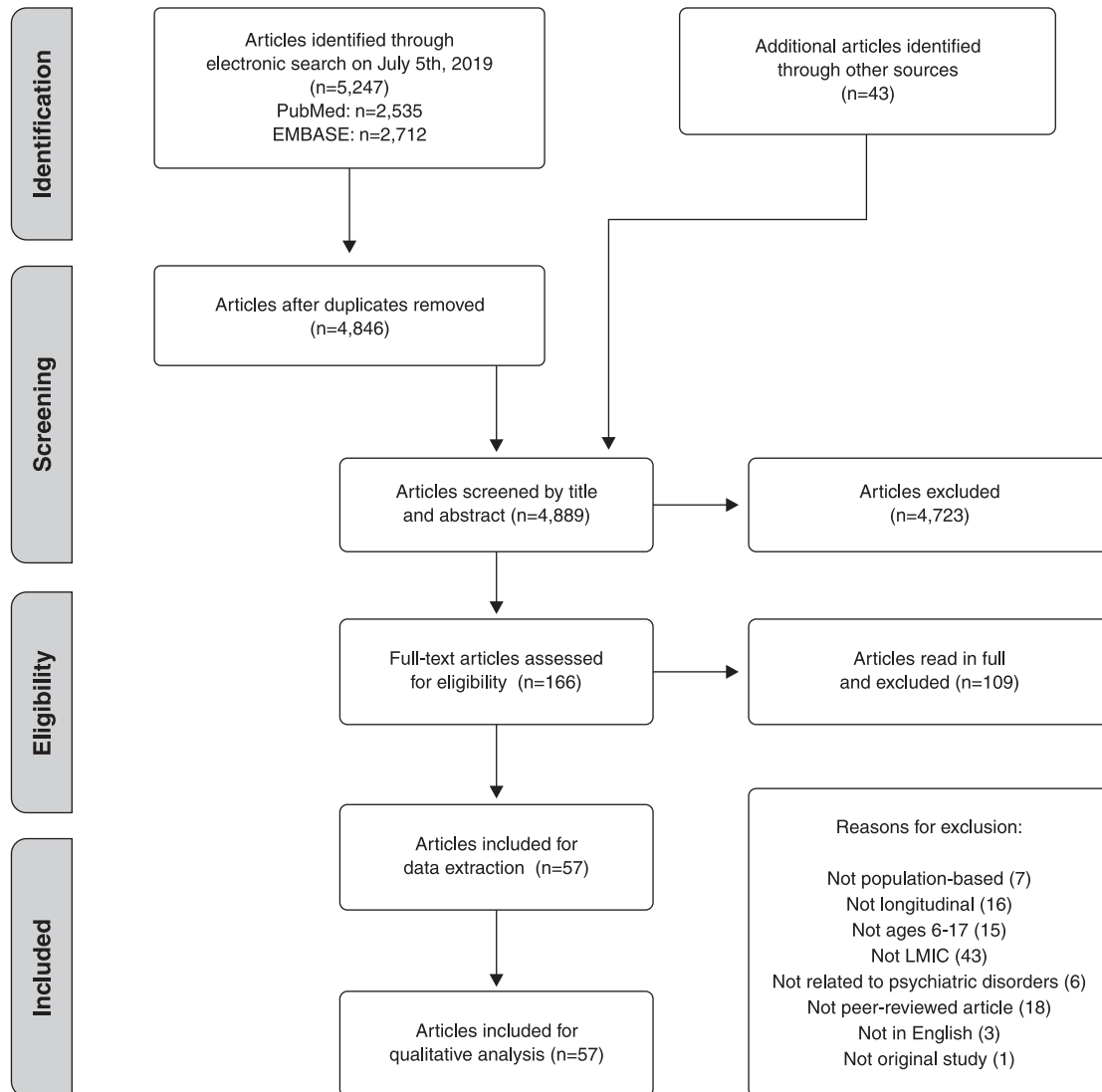
Figure 1 PRISMA flow diagram. LMIC = low- and middle-income country.

search, including the following topics: genes associated with ADHD symptoms in adolescents,[39,40] gene-environment interaction on externalizing problems in adolescents,[41] the effects of socioeconomic changes on psychopathology in adolescents,[25] the prevalence of psychopathology in 11-year-olds,[42] the continuity of behavioral and emotional problems from childhood into pre-adolescence,[43] adverse childhood experiences and alcohol, tobacco, and drug use,[44] and determinants of attention and hyperactivity problems in adolescents.[26] Thirteen studies from the 2004 Pelotas Birth Cohort were included from our search, including the following topics: the effects of early hospitalization on psychiatric disorders in children and pre-adolescents,[45] the prevalence of psychiatric disorders in children/pre-adolescents,[28,29] risk factors for disruptive mood dysregulation disorder,[46] ADHD associations,[47-49] maternal mood disorders/symptoms and child psychopathology,[50,51] intrauterine exposure and emotional/hyperactivity problems,[30] breastfeeding and mental health in children,[52]

gestational age at birth and behavioral problems,[53] and bed-sharing and psychiatric disorders in children.[54]

The Hong Kong Children of 1997 is a birth cohort study conducted in China that covers a wide range of health issues in children and adolescents, including mental health. Our search resulted in seven studies from this cohort, which comprised the following topics: how behavior problems and self-esteem are related to depression in adolescents,[32] mode of delivery and psychological problems in children and adolescents,[55] the onset of puberty and depression in adolescents,[33] second-hand smoke exposure and mental health in adolescents,[56] child care and mental health in adolescents,[57] life-course adiposity and depression in adolescents,[58] and breastfeeding and mental health in adolescents.[59]

The Birth to Twenty cohort is a birth cohort conducted in South Africa that also covers a wide range of health issues in children and adolescents, including mental health. Two studies from this cohort were included: one on

Table 1 Study design and examples findings from each cohort

Cohort	Country	Study design	Examples of findings
High-Risk Cohort Study for the Development of Childhood Psychiatric Disorders	Brazil	From a screening phase of 9,937 subjects (6 to 14 years of age), a total of 2,512 (958 randomly selected and 1,554 at high risk for mental disorders defined by symptoms and family history) were selected for further detailed evaluation (parental and child interviews and cognitive testing). Saliva samples were collected from trios of index subjects. A subsample of 720 underwent multimodal MRI techniques including T1-weighted structural, diffusion tension imaging, and resting-state functional connectivity, as well as blood sampling for biomarker evaluation.[10]	- Atypical ventral striatum functional connectivity predicted future risk for depressive disorder.[11] - Systemic inflammation may be involved in the pathway linking familial risk and mental health problems in children.[12]
1993 Pelotas Birth Cohort	Brazil	A total of 5,249 subjects were enrolled at birth and subsamples were followed up at 1, 3, and 6 months and 1, 4, 6, 9, and 12-13 years of age. All subjects were followed up at 11 and 15 years of age. Data was collected from questionnaires and interviews, and DNA was extracted from saliva.[23,24]	- Poverty was associated with more conduct problems and, to a lesser extent, emotional problems in adolescents.[25] - Attention and hyperactivity problems at age 11 were associated with male gender, low family income, smoking during pregnancy, maternal psychiatric disorder, and behavioral/emotional problems at age 4.[26]
2004 Pelotas Birth Cohort	Brazil	A total of 4,231 subjects were enrolled at birth and all were followed up at 3, 12, 24, and 48 months and 6-7 and 11 years of age. Data was collected from questionnaires and interviews.[27]	- The prevalence of psychiatric disorders was higher in boys than girls at ages 6 and 11.[28,29] - Intrauterine exposure to acetaminophen was associated with emotional and hyperactivity/ inattention problems in boys at age 6 and less so at age 11.[30]
Hong Kong Children of 1997	China	A total of 8,327 subjects were enrolled at birth and followed up through age 13. Data was collected from self-report questionnaires and clinical measurements.[31]	- Childhood behavioral problems and low self-esteem predicted adolescent depressive symptoms.[32] - Early onset of breast development was associated with higher risk of depression.[33]
Birth to Twenty	South Africa	A total of 3,273 subjects were enrolled at birth and followed up at 6 months and 1, 2, 3-4, 5, 7-8, 9-10, 11-12, 13, 14, and 15 years of age. Data was collected from questionnaires, interview, and clinical measurements.[34]	- Maternal postnatal depression was associated with adverse psychological outcomes in children at age 10.[35]
Mauritius Child Health Study	Mauritius	A total of 1,795 subjects were enrolled at age 3 and followed up at ages 8, 11, and 17. Of these subjects, 200 were selected and studied more intensely at ages 4,5,6, and 8. Data was collected from clinical assessments and checklists for behavior problems.[36]	- Malnutrition at age 3 predicted externalizing behavior problems at ages 8, 11, and 17.[37] - Birth complications are associated with increased externalizing behavior at age 11.[38]

MRI = magnetic resonance imaging.

maternal depression and psychological outcomes at age 10,[35] and one on low birth weight and emotional and behavioral outcomes at age 12.[60]

Finally, we found the Mauritius Child Health Study, a cohort study assessing child and adolescent health outcomes from age 3. Seven studies from this cohort were included: two on aggression,[61,62] one on antisocial behavior,[63] two on externalizing behavior,[37,38] one on conduct disorder,[64] and one on schizotypal personality.[65]

Discussion

Our search yielded three cohorts from Brazil, one from China, one from South Africa, and one from Mauritius. Each study produced significant findings on the development of psychiatric disorders in children and adolescents

that have contributed to the fields of psychiatry, neuroscience, and psychiatric epidemiology.

The following two papers produced from the HRC demonstrate the high-quality results that are achieved from utilizing this longitudinal epidemiological study design and the potential impact of these results:

Pan et al.[11] was the first study to link aberrant connectivity in the ventral striatum as a predictor of MDD using HRC data. Depression incidence rises from late childhood to early adolescence. Interestingly, this is also an important period for maturation of the brain's reward-processing systems. Using this large community-based sample, the authors used a discovery and replication procedure, dividing the cohort by study site, to establish a functional magnetic resonance imaging (fMRI) resting-state brain network consisting of reward-related brain

regions. Baseline functional connectivity within this resting-state reward network was then associated with clinical depression after 3 years of follow-up. They analyzed fMRI from 637 subjects aged 6-12 years at baseline. The results showed that left striatal node strength, a measure of how a specific node is connected within the entire network, predicted depressive disorder onset at follow-up, even when subjects depressed at baseline were excluded. Moreover, this finding was specific for depression, since higher striatal node strength did not predict other common adolescent psychopathologies (such as anxiety, attention-deficit/hyperactivity disorder, or substance use). These results are important because they show, for the first time, that aberrant connectivity within the reward network already occurs before the clinical diagnosis of depression. It supports the hypothesis of an impaired reward system as a fundamental etiological aspect of adolescent depression.[11]

Previous studies showed associations between polygenic risk score for Alzheimer's disease and both memory decline and lower hippocampal volume in adults. Nevertheless, studies investigating this issue in youth were lacking. The second HRC study we report herein aimed to investigate the impacts of a polygenic risk score for Alzheimer's disease on cognition and hippocampal volume in two samples of children from Brazil (N=364 and N=352) and in an additional replication sample from Canada (N=1,029). Subjects underwent genotyping, MRI, and cognitive tests. Genetic risk for Alzheimer's disease was calculated based on previous genome-wide association studies (GWAS). The authors found that, for the Brazilian samples, the genetic risk for Alzheimer's disease was associated with lower performance in both immediate and delayed recall. They also found an associations between polygenic risk score for Alzheimer's disease and lower hippocampal volume, but only for individuals with high genetic risk. Finally, they found that these association were not driven solely by the apolipoprotein E ε4 allele or by any other single nucleotide polymorphism separately, but by the aggregated genetic risk. Associations fell short of significance for the Canadian sample. These findings suggest that even neurodegenerative disorders such as Alzheimer's disease may have neurodevelopmental origins, providing further insight into Alzheimer's disease pathogenesis. This might also help advance the identification of individuals at higher risk and the development of strategies for the disease's prevention.[66]

Both of these studies show how techniques such as neuroimaging and genetics can be used to identify individuals at high risk for psychiatric disorders before a formal diagnosis would typically be made. This can be extremely useful not only for understanding how and why these disorders develop, but also to allow those at high risk to receive treatment before the disorder progresses.

There are several limitations to our study. First, it is not a comprehensive review of all cohort studies. As discussed in the methodology, we restricted our results to longitudinal cohort studies conducted in LMICs that were population-based, thus excluding studies involving specific populations.

There are many challenges in conducting longitudinal epidemiological studies involving child and adolescent psychiatry in LMICs. Some of these challenges include cost, difficulties in recruitment, loss of subjects to follow-up (largely due to lack of accessible forms of communication and incentive to participate), lack of sufficient trained personnel, issues obtaining reliable, valid data, and lack of standardized procedures for data collection and analysis.[67] Study burden is another significant barrier to participation in these types of studies, especially in LMICs where subjects may not have the means to return to the study site for follow-up; education level tends to be lower, making it more difficult and time-consuming to complete interviews; and privacy is often an issue, as subjects could face severe consequences if sensitive information is leaked. Furthermore, psychiatric disorders are often overlooked in LMICs while infectious diseases and physical chronic disorders are prioritized.

These results have significant implications for future research and practice. The scarcity of research in population neuroscience in LMICs presents an exciting opportunity for further psychiatric research utilizing a similar study design to those previously described. The ability to identify at-risk individuals can allow mental health professionals to prevent the progression of psychiatric disorders. The findings of the studies discussed herein demonstrate that there is much more research to be done at the intersection of psychiatry and neuroscience that will help to advance both fields. In addition, more effective treatments and preventive strategies can be gained by identifying biomarkers that indicate and predict key pathogenic mechanisms underlying a given disease or an individual's response to a specific treatment.[8,9] In reality, it is likely that several biomarkers should be evaluated to predict the risk of a given individual with high accuracy. The concept of risk/resilience profiling (the balance between risk and resilience factors) may serve as an alternative to prevention. Knowledge about the factors and mechanisms associated with diversity in our brain phenotypes may ultimately allow us to predict risk and prevent and mitigate suffering involved by advancing so-called personalized preventive medicine[8,9] or stratified medicine.[68] Such types of strategies are expected to be able to tremendously increase effective interventions and, consequently, improve care for psychiatric patients.

In conclusion, our results demonstrate that it is possible to conduct longitudinal cohort studies in LMICs despite challenges, and that such studies produce valuable results that help to inform the fields of psychiatry utilizing a population neuroscience strategy. This is important because these results can inspire new, innovative research and improve clinical practice in psychiatry. We encourage other LMICs to adopt this strategy and conduct similar studies in order to produce similarly valuable results and further advance these fields.

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Disclosure

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