Biological Psychiatry: CNNI

Review

Imaging Social and Environmental Factors as Modulators of Brain Dysfunction: Time to Focus on Developing Non-Western Societies

Nicolas A. Crossley, Luz Maria Alliende, Tomas Ossandon, Carmen Paz Castañeda, Alfonso González-Valderrama, Juan Undurraga, Mariana Castro, Salvador Guinjoan, Ana M. Díaz-Zuluaga, Julián A. Pineda-Zapata, Carlos López-Jaramillo, Francisco Reyes-Madrigal, Pablo León-Ortíz, Camilo de la Fuente-Sandoval, Leticia Sanguinetti Czepielewski, Clarissa S. Gama, Andre Zugman, Ary Gadelha, Andrea Jackowski, and Rodrigo Bressan

ABSTRACT

Social and environmental factors are known risk factors and modulators of mental health disorders. We here conducted a nonsystematic review of the neuroimaging literature studying the effects of poverty, urbanicity, and community violence, highlighting the opportunities of studying non-Western developing societies such as those in Latin America. Social and environmental factors in these communities are widespread and have a large magnitude, as well as an unequal distribution, providing a good opportunity for their characterization. Studying the effect of poverty in these settings could help to explore the brain effect of economic improvements, disentangle the effect of absolute and relative poverty, and characterize the modulating impact of poverty on the underlying biology of mental health disorders. Exploring urbanicity effects in highly unequal cities could help identify the specific factors that modulate this effect as well as examine a possible dose–response effect by studying megacities. Studying brain changes in those living among violence, which is particularly high in places such as Latin America, could help to characterize the interplay between brain predisposition and exposure to violence. Furthermore, exploring the brain in an adverse environment should shed light on the mechanisms underlying resilience. We finally provide examples of two methodological approaches that could contribute to this field, namely a big cohort study in the developing world and a consortium-based meta-analytic approach, and argue about the potential translational value of this research on the development of effective social policies and successful personalized medicine in disadvantaged societies.

Keywords: Developing world, Neuroimaging, Poverty, Psychiatric disorders, Urbanicity, Violence

https://doi.org/10.1016/j.bpsc.2018.09.005

Health is determined by biological factors such as genes but also by the interactions with the social and physical environment (1). Social determinants influence health at multiple levels (e.g., family, neighborhood, country) and at different times (e.g., critical stages, cumulative exposure), accounting for a large part of the existing health inequalities (2). There is an extensive literature exploring the relationship between social determinants and mental health problems. Exposure to negative social interactions, such as bullying and maltreatment, and a lack of social contact may have an enduring effect in mental health (3–5). The risk to develop psychiatric problems also depends on the wider social environment such as the similarity of people to their neighbors (6), the position within the social hierarchy (7), and the local gender policies (8). Their effect is particularly clear in migration, when the network of social ties of people is radically modified (9). The wider environment also plays a role, with the prevalence of mental health problems varying across countries (10), across urban and rural settings (11), and even with the quality of the built environment (12). While most of the evidence points to these factors increasing the risk of mental health problems, there is also evidence that they modulate the course of the illness, modifying people's response to treatment or long-term prognosis (13,14).

The brain is a highly plastic organ, continuously shaped by everyday experience, and these changes can be seen with current techniques of brain imaging (15,16). Several studies have looked at the effect of the social and physical environment in the brain, and these have been previously reviewed (17–20). We here contribute to this field by reviewing these studies from a different perspective, highlighting the importance and opportunities for non-Western developing societies. Because we are researchers based in Latin America, most of our examples are based on this region. We focus on three areas studied using neuroimaging that are particularly relevant for these communities: the effects of poverty, urbanicity, and violence. As we argue, the magnitude of these environmental

 ISSN: 2451-9022

factors and their unequal distribution in the population could provide a unique perspective. In the case of poverty, studies in these settings could explore the reversibility of brain changes after amelioration of economic deprivation, disentangle the potential role of relative and absolute poverty, and examine how poverty could modulate the underlying biology of mental health disorders. For urbanicity, the high inequality between neighborhoods could help to identify specific mechanisms mediating the urbanicity effect as well as explore the dose–response effect in megacities. In the case of violence, it could shed light on the interplay between predisposing neural factors and response to violent life events. Finally, we present ongoing approaches that could contribute to researching these factors in these communities and discuss the potential translational value of these studies.

POVERTY AND THE BRAIN

The effect of poverty on the brain has mostly focused on the developing brain, particularly highlighting a potential biological disadvantage of those in the deprived context (20). Several studies have shown that growing up in poverty is related to decreases in global cortical surface and whole-brain gray matter volume in the most deprived groups. While the changes found are global, they seem to be particularly concentrated in temporal and frontal lobes (21,22) (Figure 1). The hippocampus has been one of the structures examined in detail, with its volume being decreased in poverty (21,23,24). These structural changes appear to mediate part of the known academic disadvantage of children from lower socioeconomic status (25).

Poverty affects the brain in a nonlinear way, with those in the most deprived groups experiencing the greatest changes (22). Its influence on brain development is through various factors such as increased risk of infectious diseases at a young age, poor nutrition, lower parental education, inadequate nurturing, higher parental stress, poor access to health care and education, and higher exposure to violence and pollution (26,27). All these factors are significantly higher in developing societies. More than 60% of children under 5 years old living in low-income countries are at high risk of poor development, four times higher than children from upper middle–income countries (28). Figure 1A includes the average mean household income of a few Latin American countries, highlighting that most of the children living in these communities are within the part of the curve where brain changes related to income decreases are significantly larger. Furthermore, there is evidence that the disadvantages acquired at a young age when living in poverty in the developing world persist and even may increase through adulthood (29). On the other hand, an expected large brain effect of poverty in these communities also opens the possibility of studying the brain effect of an improvement in these conditions. One could hypothesize that hippocampal volume growth in children living in extreme poverty is likely after increases in the family income, ameliorating the brain differences separating them from children raised in nondeprived settings. This is particularly plausible considering that this brain region has been shown to be plastic to other interventions, such as exercise, even in old age (30). Such changes would demonstrate that the brain effects of poverty are indeed modifiable and rule out interpretations suggesting a reverse causality between brain differences and poverty.

Comparing the brain effect of poverty across communities with different levels of deprivation could shed light on its neural mechanisms. Fewer changes at the equivalent level of wealth across communities could suggest that the brain effect of poverty is related not only to absolute poverty (material deprivation) but also to the social status given by wealth (relative poverty). As such, poverty would be related to being a subordinated group (31). Studies on animals have accumulated evidence supporting this possibility (32). Previous studies on humans have explored this dimension, asking for a subjective assessment of their position on the social ladder rather than measuring it in absolute terms through their possessions. Using this approach, they have shown changes in anterior cingulate related to social defeat in healthy subjects (33) and changes in amygdala reactivity to angry faces related to perceived parental social status (34). These results also suggest that social defeat could exert a brain effect through emotional and stress- related mechanisms. One could hypothesize that the more unequal societies are, the larger this effect of perceived social defeat is. Intercultural studies comparing similarly rich (or poor) countries with different distributions of their wealth, such as

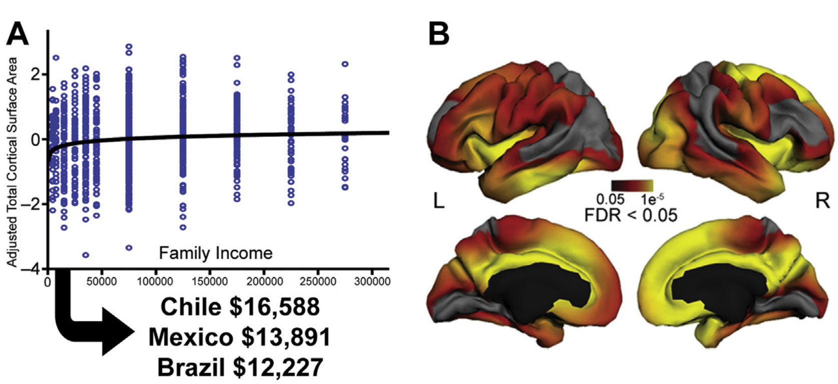

Figure 1. Brain changes seen in poverty. **(A)** Relationship between cortical surface area and family income. As shown, poverty affects particularly the most deprived groups. Data come from an American cohort (22), and for comparison mean family incomes of several Latin American countries are shown (94), highlighting that the majority of the children living in these settings would be in the part of the curve most affected by poverty. Latin American mean incomes have been corrected for purchasing power parity following the Organization for Economic Cooperation and Development methodology. This considers the different cost of living in different countries so that the amount of money listed would buy the same representative basket of consumer goods and services in the United States. **(B)** Poverty affects particularly frontal and temporal regions, as shown in this panel depicting the logarithmic relationship between poverty and cortical surface (22). FDR, false discovery rate; L, left; R, right. Figure reprinted and modified with permission from Macmillan Publishers Ltd, Nature Neuroscience (22).

Norway versus the United States and Brazil versus Cuba, will help to explore this.

Studying cohorts from the developing world is also an opportunity to disentangle how poverty and mental health disorders interact. One line of evidence suggests that poverty has a causal role in the development of certain disorders. Several brain regions that are affected by a deprived upbringing are also involved in several disorders that are known to have a higher prevalence in adverse conditions. For example, functional changes that co-occur in temporal regions in poor children have been related to the higher risk of depressive illness in this group (35). Structural changes in medial frontal regions have also been suggested to mediate the relationship between depressive symptoms and socioeconomic status in young adults (36). Similarly, frontal lobe changes seen in poor children have been associated with disruptive behavioral problems and conduct disorder (37,38). This would suggest that the brain changes caused by poverty could mediate the higher risk of certain mental health disorders in these communities (39).

Poverty also has a role in modulating how we become unwell. There is some evidence that brains exposed to poverty would have less capacity to react against a new injury regardless of whether the risk of acquiring the disorder is larger in this population. For example, the impact of human immunodeficiency virus on the brain has been proposed to be modulated by socioeconomic status (40). Alzheimer's dementia affects brains differently according to people's educational level, which is part of the socioeconomic construct; those with higher education have a different trajectory in their loss of cognitive functions, with periods in which they have increased pathology at the same level of symptoms as those with lower education (41,42). Studying populations such as the developing world could help disentangle these different trajectories.

URBANICITY AND THE BRAIN

More than half of the world's population live in cities (43), and this is still a growing trend. Living in a city, as opposed to rural settings, significantly increases a person's risk of developing a mental health problem, particularly for depression and anxiety disorders (44,45). Urban upbringing has been a main focus for a neurodevelopmental disorder such as schizophrenia (46), with Danish cohorts showing a higher risk in city-dwelling children (47,48). This effect is not as clear in epidemiological studies in lower- and middle-income countries (49), and it has been suggested that the urbanicity effect appears with increasing industrialization (50). Imaging studies have shed light on how urbanicity modifies the brain, showing that an urban upbringing is related to changes in brain areas known to be involved in the pathophysiology of schizophrenia such as the dorsolateral prefontal cortex (51). Furthermore, social stress has been suggested to be the link between urbanicity and psychosis. A previous study showed that living in a city increases amygdala reactivity to general stress, while urban upbringing during early age leaves a lasting impact on how we specifically process social stress, as indexed by a differential activation in the anterior cingulate in functional magnetic resonance imaging (52) (Figure 2A).

While social stress is a potential mediator of the urbanicity effect, it is likely that other factors, such as overcrowding,

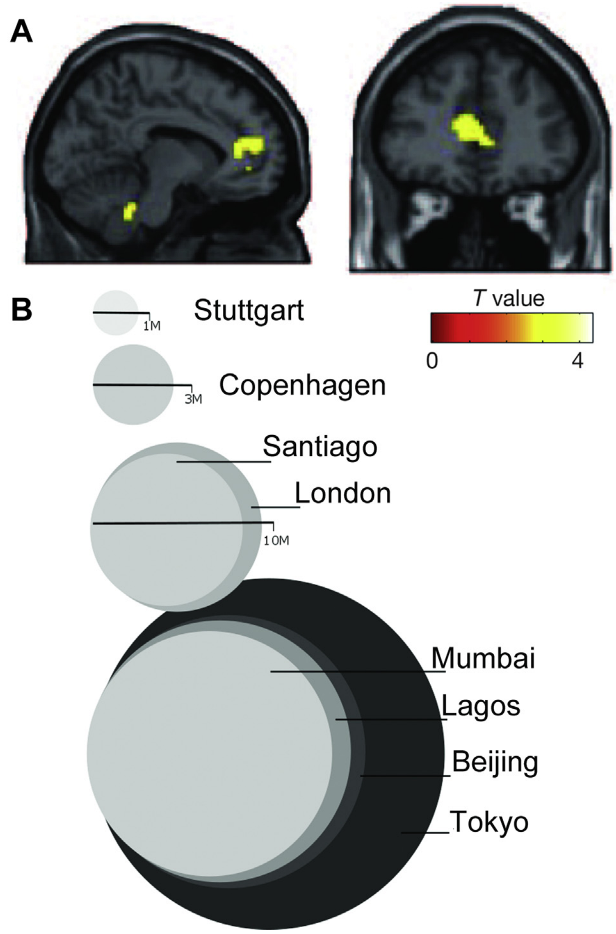

Figure 2. Brain changes related to urbanicity. **(A)** The anterior cingulate is differentially activated during a social stress paradigm in subjects who had an urban upbringing, suggesting that this might mediate the effect of urbanicity. Figure reproduced with permission from Macmillan Publishers Ltd, Nature (52). **(B)** Studies looking at the brain effect of urbanicity have been done in German and Scandinavian cities, but little is known about megacities of more than 10 million inhabitants that currently exist in many parts of the non-Western developing world (area of each circle shown is proportional to its population). M, million.

violence, contamination, and even the quality of the built environment, also play a role (12). Cities in the developing world are highly unequal in the distribution of many of these potential factors among their neighborhoods. It is not unusual to have pockets within a city where people live with economic and health standards that are similar to those in the developed world, standards that dramatically fall within just a few blocks. That increased variance within a city of potential factors causing the urbanicity effect could help in unraveling its mechanisms.

Another area in which imaging studies in the developing world can contribute is the brain effect of megacities, that is, cities with more than 10 million inhabitants (43) (Figure 2B). These megacities are mostly located in non-Western countries. More than 10% of the population in Latin America live in megacities (43). One could examine whether there is a dose–response effect of urbanicity, mirroring the higher exposure to pollution, violence, and/or inequality of its inhabitants, contributing to the understanding of its mechanisms.

COMMUNITY VIOLENCE AND THE BRAIN

Exposure to violence is a known risk factor for the development of mental health problems. This is the case for posttraumatic stress disorder (PTSD) (53) but also for anxiety, depressive, and psychotic disorders, particularly in young people (54–57). Furthermore, exposure to violence not only makes people more susceptible to developing mental health problems but also decreases response rates to different treatments across several disorders (58–60).

Community violence, defined as violent acts within the neighborhood or community but outside people's homes, has a significant impact on mental health (61). Violence is more common in specific regions of the world. More than half of the homicides in the world happen in countries that account for about 10% of the world's population, particularly Central America, South America, and South Africa (62). The high frequency of violent acts in these societies affects everyone living in them, not only subgroups whose members are the victims of these acts. There is some evidence that parents who live in a violent neighborhood are more likely to hit their children with an object (63), which increases the risk of mental health problems in those children (64).

The effect of violence in the brain has mostly been examined in clinical populations, showing decreased hippocampal volume associated with exposure to violence in PTSD (65), depression (66), and psychosis (67). Some of these brain changes might be markers of brain vulnerability that predate the exposure to violence but are picked up in case-control studies. For example, healthy twins of patients with PTSD who have not been exposed to violence also have a smaller hippocampus size (68). Cohorts in the developing world exposed to high rates of violence could be powered enough to explore this relationship. Furthermore, violence seems to have a dose–response effect on the development of mental health disorders. This has been shown for depression, where exposure to more violent life events increases the risk compared with arguably less violent events (69). This interplay between predisposing brain vulnerability and a hostile environment raises questions about the brain correlates of mental health disorders in communities surrounded by extreme violence. One could hypothesize that developing PTSD, depression, or psychosis in threatening environments might require less of a predisposing brain neuropathology.

FROM VULNERABILITY TO RESILIENCE

As we have argued, imaging studies in the developing world will be able to explore brain mechanisms of adverse socioenvironmental conditions as well as the interaction between a vulnerable brain and an adverse environment. However, not all people who are exposed to such conditions develop mental health problems. Furthermore, some evidence also points to significant structural and functional brain changes in those exposed to violence who do not necessarily develop symptoms (70,71). This raises the question about the role of resilience and protective factors. Some of these resilience factors might be characteristics of the individual, while others might be shared within the community such as the structure and type of family support. Regarding the latter, studies on children raised in poverty describe that positive family interactions prevent hippocampal volume deficits (21,72). Even support from grandparents has been shown to be beneficial for children (73). Family structure in developing world communities tends to be more extensive, perhaps partly as a response to the adverse environment (74), where support from the extended family could be the only resource people are able to access (75). Imaging studies in those communities will be able to examine whether family support buffers the brain effect of the adverse environment.

THE ROLE OF BIG COHORT STUDIES AND META-ANALYTIC APPROACHES FOR EXPLORING SOCIAL AND ENVIRONMENTAL FACTORS IN THE DEVELOPING WORLD

Social determinants of health have a large effect on our mental health. However, a relatively large sample size for imaging studies is still required to demonstrate an effect on the brain. We have discussed how big cohort studies in the developed world have shed light on the developmental effect of social determinants, and ongoing large-scale epidemiological imaging studies will also certainly contribute to the field in the future (76,77). Although expensive, a few ongoing large imaging cohort studies have started looking at brain development in the developing world, including the Bangladesh Early Adversity Neuroimaging Project (78) and the Instituto Nacional de Psiquiatria do Desenvolvimento para Crianças e Adolescentes Project (79). The latter includes 2401 children aged 6 to 12 years living in Porto Alegre and São Paulo, Brazil, with about two thirds of the sample recruited being enriched for children with a family history of mental health problems and the other one third corresponding to a random sample. A total of 750 children were invited to one magnetic resonance imaging scanning session, and a subsample was scanned again after 3 years. Nearly 70% of participating children had been exposed to traumatic life events (80), and about 20% of those scanned had a mean household monthly income lower than $230 in U.S. dollars (not corrected for purchasing power parity). Planned analyses include exploring the role of violence and socioeconomic status in brain development. Considering that two thirds of the cohort had a high family risk to develop a mental health problem, this cohort might be able to explore the brain changes related to the interplay between social factors and the development of common mental health disorders.

An alternative approach to studying the effect of social determinants on mental health disorders is to pool results from cross-sectional case-control studies, an approach that is particularly useful for less frequent disorders such as schizophrenia. This is the current proposal of ANDES (Iberoamerican Network for the Study of Early Psychosis) (81), a Latin American consortium of groups studying early psychosis, focusing on the uniqueness of becoming unwell in a highly violent and poor environment. Imaging centers included are Santiago, Chile; Buenos Aires, Argentina; Porto Alegre and São Paulo, Brazil; Medellin, Colombia; and Mexico City, Mexico. Ongoing projects have started using social factors as regressors for case-control imaging analyses, looking for an interaction between these two factors, and pooling results using meta-analytic approaches. As a consortium initially using already acquired data, missing information about social factors has been imputed from characteristics of the neighborhoods where subjects lived at the time of the assessment, taking advantage of the spatial segregation of socioeconomic status and violence within Latin American cities (82). If successful, a similar approach could be used to study the brain effects of social determinants across the world, mirroring the ENIGMA (Enhancing Neuroimaging Genetics through Meta-analysis) consortium for genetic determinants (83). Alongside the gain of power by pooling samples, the meta-analytic approach could use metaregression to explore differences across communities. For example, it could help explore the absolute/relative effect of poverty or the resilient effect of specific family structures in different communities.

TRANSLATIONAL IMPACT OF IMAGING SOCIAL DETERMINANTS

Imaging studies in developing world communities such as Latin America will be able to contribute to our understanding of the brain mechanisms of social and environmental factors. They might also inform effective public policies as well as personalized medicine approaches.

The case for improving the lives of people who are in extreme poverty or exposed to violence does not need to be supported by imaging studies. However, we and others (84) would argue that knowing how adverse environments affect the brain will help tailor protective measures. The successful story of folate supplementation in protecting brain development is an example. Imaging research has shown that supplementation at critical periods has a long-lasting impact on the brain structure (85). Imaging would also contribute to strategies trying to foster resilient mechanisms to counteract their deleterious effect, such as the modulating effect of good parenting on the hippocampal changes seen in poverty (72). We also previously mentioned the different trajectories observed with imaging in dementia according to educational level. Considering the projected impact that dementia will have in low- and middle-income countries (86), these results will stress further the need to improve education in the region. As is now recognized by institutions such as the United Nations Children's Fund, understanding what, how, and when social determinants affect the brain will help maximize children's development around the world (87). Studying the neurobiology of social factors will also contribute to our understanding of how they affect decision making. This has been particularly studied in the context of poverty and how it puts people "at risk of risks" (88) or makes them "behave poorly" (89). Understanding the mechanisms of this irrational behavior could help remediate them and support economic growth (90).

Studying the brain effect of social and environmental factors will also contribute to extending the potential biomedical benefits of new technologies to disadvantaged societies. Brain imaging has long aspired to inform the clinical management of our patients (91), and personalized medicine approaches in imaging research are bringing it closer to the bedside (92,93). However, most (if not all) of these algorithms are tested in developed societies, where these social factors have potentially less impact on the brain as we have argued. If we do not include the social and environmental factors in the algorithms, it is likely that these techniques will not work in developing societies. Perhaps they might be helpful in the subgroup of the upper classes within these societies, whose living standards are like those in the developed world. As such, understanding how social factors affect the brain will be essential for the success of these algorithms in these societies and will prevent some of the enduring inequalities in health from perpetuating.

CONCLUSIONS

Studying the brain effect of social and environmental factors using neuroimaging is an important area of research to advance in our understanding of mental health disorders. Developing world communities appear as promising settings to address these questions about social and environmental factors because of their high prevalence, high inequality in their distribution, and large effect. Understanding the social and environmental factors in brain dysfunction will help the development of more effective social policies and personalized medicine approaches in these societies.

ACKNOWLEDGMENTS AND DISCLOSURES

This work was partly supported by Programa Iberoamericano de Ciencia y Tecnología para el Desarrollo "CYTED REDES" (Grant No. 218RT0547), Comisión Nacional de Investigación Científica y Tecnológica Chile Grant No. PIA ACT1414 (to TO and NAC), Fondo Nacional de Desarrollo Científico y Tecnológico Regular Grant No. 1160736 (to NAC), and Consejo Nacional de Ciencia y Tecnología Mexico Grant Nos. 182279 and 261895 (to CdlF-S).

CdlF-S has served as a consultant for Janssen, and FR-M has served as a speaker for AstraZeneca. The other authors report no biomedical financial interests or potential conflicts of interest.

ARTICLE INFORMATION

From the Department of Psychiatry (NAC, LMA, TO), School of Medicine, and Biomedical Imaging Center and Center for Integrative Neuroscience (NAC), Pontificia Universidad Católica de Chile, Early Intervention Program (CPC, AG-V, JU), José Horwitz Psychiatric Institute, School of Medicine (AG-V), Universidad Finis Terrae, and Department of Neurology and Psychiatry (JU), Faculty of Medicine, Clínica Alemana Universidad del Desarrollo, Santiago, Chile; Department of Psychosis Studies (NAC), Institute of Psychiatry, Psychology and Neurosciences, King's College London, United Kingdom; FLENI Foundation (MC, SG) and Department of Psychiatry and Mental Health (MC, SG), School of Medicine, University of Buenos Aires, Buenos Aires, Argentina; Research Group in Psychiatry (AMD-Z, CL-J), Department of Psychiatry, Faculty of Medicine, Universidad de Antioquia, Research Group (JAP-Z), Instituto de Alta Tecnología Médica, and Mood Disorders Program (CL-J), Hospital Universitario San Vicente Fundación, Medellín, Colombia; Laboratory of Experimental Psychiatry (FR-M, PL-O, CdlF-S), Neuropsychiatry Department, Instituto Nacional de Neurología y Neurocirugía, Mexico City, Mexico; Molecular Psychiatry Laboratory (LSC, CSG), Hospital de Clinicas de Porto Alegre, Programa de Pós-Graduação em Psiquiatria e Ciências do Comportamento, Universidade Federal do Rio Grande do Sul, Porto Alegre, and Laboratory of Interdisciplinary Clinical Neuroscience (AZ, AG, AJ, RB), Department of Psychiatry, Federal University of São Paulo, São Paulo, Brazil.

Address correspondence to Nicolas A. Crossley, M.R.C.S. Psych., Ph.D., Department of Psychiatry, School of Medicine, Pontificia Universidad Católica de Chile, Diagonal Paraguay 362, 5to Piso, Oficina 543, Santiago, Chile 8330077; E-mail: ncrossley@uc.cl.

Received Jun 14, 2018; revised Sep 13, 2018; accepted Sep 14, 2018.

REFERENCES

1. Marmot M, Allen J, Bell R, Bloomer E, Goldblatt P; Consortium for the European Review of Social Determinants of Health and the Health Divide (2012): WHO European review of social determinants of health and the health divide. Lancet 380(9846):1011–1029.
2. Hernandez LM, Blazer DG (2006): Institute of Medicine (US) Committee on Assessing Interactions Among Social Behavioral and Genetic Factors in Health. Genes, Behavior, and the Social Environment: Moving Beyond the Nature/Nurture Debate. Washington, DC: National Academies Press.
3. Scott KM, Smith DR, Ellis PM (2010): Prospectively ascertained child maltreatment and its association with DSM-IV mental disorders in young adults. Arch Gen Psychiatry 67:712–719.
4. Takizawa R, Maughan B, Arseneault L (2014): Adult health outcomes of childhood bullying victimization: Evidence from a five-decade longitudinal British birth cohort. Am J Psychiatry 171:777–784.
5. Donovan NJ, Okereke OI, Vannini P, Amariglio RE, Rentz DM, Marshall GA, *et al.* (2016): Association of higher cortical amyloid burden with loneliness in cognitively normal older adults. JAMA Psychiatry 73:1230–1237.
6. Kirkbride JB, Jones PB, Ullrich S, Coid JW (2014): Social deprivation, inequality, and the neighborhood-level incidence of psychotic syndromes in East London. Schizophr Bull 40:169–180.
7. Murphy JM, Olivier DC, Monson RR, Sobol AM, Federman EB, Leighton AH (1991): Depression and anxiety in relation to social status: A prospective epidemiologic study. Arch Gen Psychiatry 48:223–229.
8. Yu S (2018): Uncovering the hidden impacts of inequality on mental health: A global study. Transl Psychiatry 8:98.
9. Cantor-Graae E, Selten JP (2005): Schizophrenia and migration: A meta-analysis and review. Am J Psychiatry 162:12–24.
10. Ruscio AM, Hallion LS, Lim CCW, Aguilar-Gaxiola S, Al-Hamzawi A, Alonso J, *et al.* (2017): Cross-sectional comparison of the epidemiology of DSM-5 generalized anxiety disorder across the globe. JAMA Psychiatry 74:465–475.
11. Vassos E, Pedersen CB, Murray RM, Collier DA, Lewis CM (2012): Meta-analysis of the association of urbanicity with schizophrenia. Schizophr Bull 38:1118–1123.
12. Araya R, Montgomery A, Rojas G, Fritsch R, Solis J, Signorelli A, Lewis G (2007): Common mental disorders and the built environment in Santiago, Chile. Br J Psychiatry 190:394–401.
13. Melchior M, Chastang JF, Head J, Goldberg M, Zins M, Nabi H, Younès N (2013): Socioeconomic position predicts long-term depression trajectory: A 13-year follow-up of the GAZEL cohort study. Mol Psychiatry 18:112–121.
14. Chen YR, Swann AC, Burt DB (1996): Stability of diagnosis in schizophrenia. Am J Psychiatry 153:682–686.
15. Mechelli A, Crinion JT, Noppeney U, O'Doherty J, Ashburner J, Frackowiak RS, Price CJ (2004): Neurolinguistics: Structural plasticity in the bilingual brain. Nature 431:757.
16. Draganski B, Gaser C, Busch V, Schuierer G, Bogdahn U, May A (2004): Changes in grey matter induced by training. Nature 427:311–312.
17. Tost H, Champagne FA, Meyer-Lindenberg A (2015): Environmental influence in the brain, human welfare and mental health. Nat Neurosci 18:1421–1431.
18. Lambert KG, Nelson RJ, Jovanovic T, Cerdá M (2015): Brains in the city: Neurobiological effects of urbanization. Neurosci Biobehav Rev 58:107–122.
19. Krabbendam L, Hooker CI, Aleman A (2014): Neural effects of the social environment. Schizophr Bull 40:248–251.
20. Farah MJ (2017): The neuroscience of socioeconomic status: Correlates, causes, and consequences. Neuron 96:56–71.
21. Luby J, Belden A, Botteron K, Marrus N, Harms MP, Babb C, *et al.* (2013): The effects of poverty on childhood brain development. JAMA Pediatr 167:1135–1142.
22. Noble KG, Houston SM, Brito NH, Bartsch H, Kan E, Kuperman JM, *et al.* (2015): Family income, parental education and brain structure in children and adolescents. Nat Neurosci 18:773–778.
23. Hanson JL, Chandra A, Wolfe BL, Pollak SD (2011): Association between income and the hippocampus. PLoS One 6:e18712.
24. Yu Q, Daugherty A, Anderson D, Nishimura M, Brush D, Hardwick A, *et al.* (2018): Socioeconomic status and hippocampal volume in children and young adults. Dev Sci 21:e12561.
25. Hair NL, Hanson JL, Wolfe BL, Pollak SD (2015): Association of child poverty, brain development, and academic achievement. JAMA Pediatr 169:822–829.
26. Niehaus MD, Moore SR, Patrick PD, Derr LL, Lorntz B, Lima AA, Guerrant RL (2002): Early childhood diarrhea is associated with diminished cognitive function 4 to 7 years later in children in a northeast Brazilian shantytown. Am J Trop Med Hyg 66:590–593.
27. Patel V, Rahman A, Jacob KS, Hughes M (2004): Effect of maternal mental health on infant growth in low income countries: New evidence from South Asia. Br Med J 328:820–823.
28. Lu C, Black MM, Richter LM (2016): Risk of poor development in young children in low-income and middle-income countries: An estimation and analysis at the global, regional, and country level. Lancet Glob Health 4:e916–e922.
29. Paxson C, Schady N (2014): Cognitive development among young children in Ecuador: The roles of wealth and parenting. J Hum Resour 42:49–84.
30. Erickson KI, Voss MW, Prakash RS, Basak C, Szabo A, Chaddock L, *et al.* (2011): Exercise training increases size of hippocampus and improves memory. Proc Natl Acad Sci U S A 108:3017–3022.
31. Selten JP, van der Ven E, Rutten BPF, Cantor-Graae E (2013): The social defeat hypothesis of schizophrenia: An update. Schizophr Bull 39:1180–1186.
32. Cavigelli SA, Chaudhry HS (2012): Social status, glucocorticoids, immune function, and health: Can animal studies help us understand human socioeconomic-status-related health disparities? Horm Behav 62:295–313.
33. Gianaros PJ, Horenstein JA, Cohen S, Matthews KA, Brown SM, Flory JD, *et al.* (2007): Perigenual anterior cingulate morphology covaries with perceived social standing. Soc Cogn Affect Neurosci 2:161–173.
34. Gianaros PJ, Horenstein JA, Hariri AR, Sheu LK, Manuck SB, Matthews KA, Cohen S (2008): Potential neural embedding of parental social standing. Soc Cogn Affect Neurosci 3:91–96.
35. Barch D, Pagliaccio D, Belden A, Harms MP, Gaffrey M, Sylvester CM, *et al.* (2016): Effect of hippocampal and amygdala connectivity on the relationship between preschool poverty and school-age depression. Am J Psychiatry 173:625–634.
36. Yang J, Liu H, Wei D, Liu W, Meng J, Wang K, *et al.* (2016): Regional gray matter volume mediates the relationship between family socioeconomic status and depression-related trait in a young healthy sample. Cogn Affect Behav Neurosci 16:51–62.
37. Hanson JL, Hair N, Shen DG, Shi F, Gilmore JH, Wolfe BL, Pollak SD (2013): Family poverty affects the rate of human infant brain growth. PLoS One 8:e80954.
38. Holz NE, Boecker R, Hohm E, Zohsel K, Buchmann AF, Blomeyer D, *et al.* (2015): The long-term impact of early life poverty on orbitofrontal cortex volume in adulthood: Results from a prospective study over 25 years. Neuropsychopharmacology 40:996–1004.
39. Patel V, Kleinman A (2003): Poverty and common mental disorders in developing countries. Bull World Health Organ 81:609–615.
40. Arentoft A, Byrd D, Monzones J, Coulehan K, Fuentes A, Rosario A, *et al.* (2015): Socioeconomic status and neuropsychological functioning: Associations in an ethnically diverse HIV+ cohort. Clin Neuropsychol 29:232–254.
41. Stern Y, Alexander GE, Prohovnik I, Stricks L, Link B, Lennon MC, *et al.* (1995): Relationship between lifetime occupation and parietal flow: Implications for a reserve against Alzheimer's disease pathology. Neurology 45:55–60.
42. Amieva H, Mokri H, Le Goff M, Meillon C, Jacqmin-Gadda H, Foubert-Samier A, *et al.* (2014): Compensatory mechanisms in higher-educated subjects with Alzheimer's disease: A study of 20 years of cognitive decline. Brain 137:1167–1175.

43. United Nations, Department of Economic and Social Affairs, Population Division (2015): World Urbanization Prospects 2014. New York: United Nations.
44. Blazer D, George LK, Landerman R, Pennybacker M, Melville M Lou, Woodbury M, *et al.* (1985): Psychiatric disorders: A rural/urban comparison. Arch Gen Psychiatry 42:651–656.
45. Peen J, Schoevers RA, Beekman AT, Dekker J (2010): The current status of urban-rural differences in psychiatric disorders. Acta Psychiatr Scand 121:84–93.
46. Rapoport JL, Giedd JN, Gogtay N (2012): Neurodevelopmental model of schizophrenia: Update 2012. Mol Psychiatry 17:1228–1238.
47. Pedersen CB, Mortensen PB (2001): Evidence of a dose-response relationship between urbanicity during upbringing and schizophrenia risk. Arch Gen Psychiatry 58:1039–1046.
48. Mortensen PB, Pedersen CB, Westergaard T, Wohlfahrt J, Ewald H, Mors O, *et al.* (1999): Effects of family history and place and season of birth on the risk of schizophrenia. N Engl J Med 340:603–608.
49. DeVylder JE, Kelleher I, Lalane M, Oh H, Link BG, Koyanagi A (2018): Association of urbanicity with psychosis in low- and middle-income countries. JAMA Psychiatry 75:678–686.
50. Chan KY, Zhao FF, Meng S, Demaio AR, Reed C, Theodoratou E, *et al.* (2015): Urbanization and the prevalence of schizophrenia in China between 1990 and 2010. World Psychiatry 14:251–252.
51. Haddad L, Schäfer A, Streit F, Lederbogen F, Grimm O, Wüst S, *et al.* (2015): Brain structure correlates of urban upbringing, an environmental risk factor for schizophrenia. Schizophr Bull 41:115–122.
52. Lederbogen F, Kirsch P, Haddad L, Streit F, Tost H, Schuch P, *et al.* (2011): City living and urban upbringing affect neural social stress processing in humans. Nature 474:498–501.
53. Breslau N, Davis GC, Andreski P, Peterson E (1991): Traumatic events and posttraumatic stress disorder in an urban population of young adults. Arch Gen Psychiatry 48:216–222.
54. Schwab-Stone M, Chen C, Greenberger E, Silver D, Lichtman J, Voyce C (1999): No safe haven: II. The effects of violence exposure on urban youth. J Am Acad Child Adolesc Psychiatry 38:359–367.
55. Singer MI, Song LY, Lunghofer L, Anglin TM (1995): Adolescents' exposure to violence and associated symptoms of psychological trauma. JAMA 273:477–482.
56. Murray J, Lima NP, Ruivo ACO, Ramírez Varela A, Bortolotto CC, Magalhães EIDS, *et al.* (2018): Lifelong robbery victimisation and mental disorders at age 18 years: Brazilian population-based study. Soc Psychiatry Psychiatr Epidemiol 53:487–496.
57. Newbury J, Arseneault L, Caspi A, Moffitt TE, Odgers CL, Fisher HL (2018): Cumulative effects of neighborhood social adversity and personal crime victimization on adolescent psychotic experiences. Schizophr Bull 44:348–358.
58. Hassan AN, De Luca V (2015): The effect of lifetime adversities on resistance to antipsychotic treatment in schizophrenia patients. Schizophr Res 161:496–500.
59. Lewis CC, Simons AD, Nguyen LJ, Murakami JL, Reid MW, Silva SG, March JS (2010): Impact of childhood trauma on treatment outcome in the Treatment for Adolescents with Depression Study (TADS). J Am Acad Child Adolesc Psychiatry 49:132–140.
60. Shamseddeen W, Asarnow JR, Clarke GN, Vitiello B, Wagner KD, Birmaher B, *et al.* (2011): Impact of physical and sexual abuse on treatment response in the Treatment of Resistant Depression in Adolescent Study (TORDIA). J Am Acad Child Adolesc Psychiatry 50:293–301.
61. Fowler PJ, Tompsett CJ, Braciszewski JM, Jacques-Tiura AJ, Baltes BB (2009): Community violence: A meta-analysis on the effect of exposure and mental health outcomes of children and adolescents. Dev Psychopathol 21:227–259.
62. United Nations, Office on Drugs and Crime (2013): Global Study on Homicide 2013: Trends, Contexts, Data New York: United Nations.
63. Cuartas J (2018): Neighborhood crime undermines parenting: Violence in the vicinity of households as a predictor of aggressive discipline. Child Abuse Negl 76:388–399.
64. Fleitlich B, Goodman R (2001): Social factors associated with child mental health problems in Brazil: Cross sectional survey. BMJ 323:599–600.
65. Logue MW, van Rooij SJH, Dennis EL, Davis SL, Hayes JP, Stevens JS, *et al.* (2018): Smaller hippocampal volume in posttraumatic stress disorder: A multisite ENIGMA-PGC study: Subcortical volumetry results from posttraumatic stress disorder consortia. Biol Psychiatry 83:244–253.
66. Vythilingam M, Heim C, Newport J, Miller AH, Anderson E, Bronen R, *et al.* (2002): Childhood trauma associated with smaller hippocampal volume in women with major depression. Am J Psychiatry 159:2072–2080.
67. Hoy K, Barrett S, Shannon C, Campbell C, Watson D, Rushe T, *et al.* (2012): Childhood trauma and hippocampal and amygdalar volumes in first-episode psychosis. Schizophr Bull 38:1162–1169.
68. Gilbertson MW, Shenton ME, Ciszewski A, Kasai K, Lasko NB, Orr SP, Pitman RK (2002): Smaller hippocampal volume predicts pathological vulnerability to psychological trauma. Nat Neurosci 5:1242–1247.
69. Kendler KS, Karkowski LM, Prescott CA (1999): Causal relationship between stressful life events and the onset of major depression. Am J Psychiatry 156:837–841.
70. Calem M, Bromis K, McGuire P, Morgan C, Kempton MJ (2017): Meta-analysis of associations between childhood adversity and hippocampus and amygdala volume in non-clinical and general population samples. Neuroimage Clin 14:471–479.
71. Sharot T, Martorella EA, Delgado MR, Phelps EA (2007): How personal experience modulates the neural circuitry of memories of September 11. Proc Natl Acad Sci U S A 104:389–394.
72. Brody GH, Gray JC, Yu T, Barton AW, Beach SRH, Galvan A, *et al.* (2017): Protective prevention effects on the association of poverty with brain development. JAMA Pediatr 171:46–52.
73. Pope SK, Whiteside L, Brooks-Gunn J, Kelleher KJ, Rickert VI, Bradley RH, Casey PH (1993): Low-birth-weight infants born to adolescent mothers: Effects of coresidency with grandmother on child development. JAMA 269:1396–1400.
74. Angel R, Tienda M (1982): Determinants of extended household structure: Cultural pattern or economic need? Am J Sociol 87:1360–1383.
75. Brockington I, Chandra P, Dubowitz H, Jones D, Moussa S, Nakku J, Ferre IQ (2011): WPA guidance on the protection and promotion of mental health in children of persons with severe mental disorders. World Psychiatry 10:93–102.
76. White T, Muetzel RL, El Marroun H, Blanken LME, Jansen P, Bolhuis K, *et al.* (2018): Paediatric population neuroimaging and the Generation R Study: The second wave. Eur J Epidemiol 33:99–125.
77. Miller KL, Alfaro-Almagro F, Bangerter NK, Thomas DL, Yacoub E, Xu J, *et al.* (2016): Multimodal population brain imaging in the UK Biobank prospective epidemiological study. Nat Neurosci 19:1523–1536.
78. Nelson CA (2015): An international approach to research on brain development. Trends Cogn Sci 19:424–426.
79. Salum GA, Gadelha A, Pan PM, Moriyama TS, Graeff-Martins AS, Tamanaha AC, *et al.* (2015): High risk cohort study for psychiatric disorders in childhood: Rationale, design, methods and preliminary results. Int J Methods Psychiatr Res 24:58–73.
80. Moriyama TS, Drukker M, Gadelha A, Pan PM, Salum GA, Manfro GG, *et al.* (2018): The association between psychotic experiences and traumatic life events: The role of the intention to harm. Psychol Med 48:2235–2246.
81. Programa Iberoamericano de Ciencia y Tecnología para el Desarrollo. Red Iberoamericana para el Estudio de la Psicosis Precoz (ANDES). Available at: http://www.cyted.org/es/andes. Accessed June 13, 2018.
82. Lungo M, Baires S (2001): Socio-spatial segregation and urban land regulation in Latin American cities. Presented at "Segregation in the City" seminar, Lincoln Institute of Land Policy, July 25–28, Cambridge, MA.
83. Thompson PM, Stein JL, Medland SE, Hibar DP, Vasquez AA, Renteria ME, *et al.* (2014): The ENIGMA Consortium: Large-scale collaborative analyses of neuroimaging and genetic data. Brain Imaging Behav 8:153–182.
84. Farah MJ (2018): Socioeconomic status and the brain: Prospects for neuroscience-informed policy. Nat Rev Neurosci 19:428–438.

85. Eryilmaz H, Dowling KF, Huntington FC, Rodriguez-Thompson A, Soare TW, Beard LM, *et al.* (2018): Association of prenatal exposure to population-wide folic acid fortification with altered cerebral cortex maturation in youths. JAMA Psychiatry 75:918–928.
86. Gulland A (2012): Number of people with dementia will reach 65.7 million by 2030, says report. BMJ 344:e2604.
87. United Nations Children's Fund (2014): Building Better Brains: New Frontiers in Early Childhood Development. New York: United Nations. Available at: http://www.unicef.cn/en/index.php?m=content&c=index&a=show&catid=220&id=2189.
88. Link BG, Phelan J (1995): Social conditions as fundamental causes of disease. J Health Soc Behav 35:80–94.
89. Lynch JW, Kaplan GA, Salonen JT (1997): Why do poor people behave poorly? Variation in adult health behaviours and psychosocial characteristics by stages of the socioeconomic lifecourse. Soc Sci Med 44:809–819.
90. World Bank (2015): World Development Report 2015: Mind, Society, and Behavior. Washington, DC: World Bank. https://doi.org/10.1596/978-1-4648-0342-0.
91. Kapur S, Phillips a G, Insel TR (2012): Why has it taken so long for biological psychiatry to develop clinical tests and what to do about it? Mol Psychiatry 17:1174–1179.
92. Gifford G, Crossley N, Fusar-Poli P, Schnack HG, Kahn RS, Koutsouleris N, *et al.* (2017): Using neuroimaging to help predict the onset of psychosis. NeuroImage 145:209–217.
93. Dwyer DB, Falkai P, Koutsouleris N (2018): Machine learning approaches for clinical psychology and psychiatry. Annu Rev Clin Psychol 14:91–118.
94. Organization for Economic Cooperation and Development. OECD Better Life Index. Available at: http://www.oecdbetterlifeindex.org. Accessed August 5, 2018.