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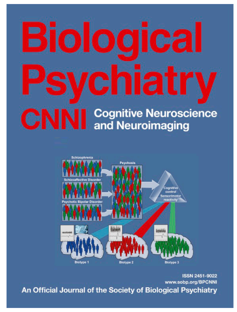

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Imaging social and environmental factors as modulators of brain dysfunction: time to focus on developing, non-Western societies

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Abstract

Social and environmental factors are known risk factors and modulators of mental health disorders. We here conducted a non-systematic 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 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 examining a possible dose-response by studying mega-cities. Studying brain changes in those living among violence, which is particularly high in places such as Latin America, could help characterize the interplay between brain predisposition and exposure to violence. Furthermore, exploring the brain in an adverse environment will 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.

- Introduction

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 (i.e., family, neighborhood or country) and at different times (critical stages, cumulative exposure), accounting for 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 or maltreatment, or a lack of social contact, may both 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 the person to their neighbors (6), the position within the social hierarchy (7), or the local gender policies (8). Their effect is particularly clear in migration, when the network of social ties of the person is radically modified (9). The wider environment also plays a role, with the prevalence of mental health problems varying across countries (10), 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 their 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, which have been previously reviewed (17–20). We would like to contribute to this field by reviewing these studies from a different perspective, highlighting the importance and opportunities for non-Western, developing societies. As researchers based in Latin America, most of our examples will be based on this region. We will focus on three areas studied using neuroimaging that are particularly relevant for these communities: the effect of poverty, urbanicity, and violence. As we will argue, the magnitude of these environmental 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 identify specific mechanisms mediating the urbanicity effect, as well as exploring the dose-response effect in mega-cities. In the case of violence, it could shed light on the interplay between predisposing neural factors and response to violent life events. Finally, we would like to 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 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 non-linear way, with those in the most deprived group experiencing the greatest changes (22). Its influence on brain development is through different factors, such as increased risk of infectious diseases at young age, poor nutrition, lower parental education, inadequate nurturing, higher parental stress, poor access to healthcare and education, higher exposure to violence and pollution, etc... (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 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 are likely after increases in the family income, ameliorating the brain differences separating them from children raised in non-deprived 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. Less changes at the equivalent level of wealth across communities could suggest that the brain effect of poverty is not only related 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 study on humans have explored this dimension asking for a subjective assessment of their position in 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 the 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, perhaps the larger this effect of perceived social defeat. Intercultural studies comparing similarly rich (or poor) countries with different distribution of their wealth, such as Norway and the USA, or Brazil and Cuba, will help 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, which 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 to disruptive 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, irrespective if the risk of acquiring the disorder is larger in this population. For example, the impact of HIV on the brain has been proposed to be modulated by socioeconomic status (40). Alzheimer’s dementia affects brains differently according to their 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 to those with lower education (41, 42). Studying populations such as the developing world could help disentangling 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 your 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 or 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 has shown that living in a city increases amygdala reactivity to general stress, while urban upbringing during early age leaves a lasting impact in how we specifically process social stress, as indexed by a differential activation in the anterior cingulate in functional MRI (52) (**Figure 2A)**.

While social stress is a potential mediator of the urbanicity effect, it is likely that other factors also play a role, such as overcrowding, violence, contamination, or even the quality of the built environment (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 the city where people live with economic and health standards that are similar to the developed world, standards which dramatically fall within just a few blocks. That increased variance within a city of potential factors causing the urbanicity effect could help in unravelling its mechanisms.

Another area in which imaging studies in the developing world can contribute is the brain effect of mega-cities, that is cities with over 10 million inhabitants (43)(**Figure 2B**). These mega-cities are mostly located in non-Western countries. More than 10% of the population in Latin American live in one (43). One could examine whether there is a dose-response effect of urbanicity, mirroring the higher exposure to pollution, violence, 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 post-traumatic stress disorder (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 develop mental health problems, but it 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, have a significant impact in mental health (61). Unfortunately, violence is more common in specific regions of the world. Over half of the homicides in the world happen in countries which account for around 10% of the world's population, particularly Central and South America, and South Africa (62). The high frequency of violent acts in these societies affects everyone living in them, not only subgroups who 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 PTSD-patients, 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. Furthermore, violence seems to have a dose-response on the development of mental health disorders. This has been shown for depression, where exposure to more violent life events increase the risk compared to 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 socio-environmental 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 out 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, 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 tend to be more extensive, partly perhaps as a response to the adverse environment (74), where support from the extended family could be the only resource people might be 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 in 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 big imaging cohort studies have started looking at brain development in the developing world, such as the Bangladesh Early Adversity Neuroimaging Project (78), or the Instituto Nacional de Psiquiatria do Desenvolvimento para Crianças e Adolescentes Project (INPD) in Brazil (79). The latter includes 2401 children aged 6-12 years old living in Porto Alegre and São Paulo, Brazil, with around 2/3 of the sample being enriched for children with a family history of mental health problems, and the other 1/3 corresponding to a random sample. 750 children have been invited to one MRI scanning session, and a subsample has been scanned again after 3 years. Almost 70% of participating children had been exposed to traumatic life events (80), and around 20% of those scanned had a mean household monthly income lower than $230 USD (not corrected for purchasing power parity). Planned analyses include exploring the role of violence and socioeconomic status on brain development. Considering that the cohort was enriched for those children with 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, which is particularly useful for the less frequent disorders such as schizophrenia. This is the current proposal of the Iberoamerican Network for the Study of Early Psychosis ANDES (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, Buenos Aires, Porto Alegre, São Paulo, Medellin and Mexico City. 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 consortium for genetic determinants (83). Alongside the gain of power by pooling samples, the meta-analytic approach could use meta-regression 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 people's lives 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 of that. Nutritional deficits can be varied, yet imaging research has shown that when supplemented at critical periods it 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 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 UNICEF, 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) these algorithms are tested in developed societies, where these social factors have potentially lesser 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 on 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 hinder some of the enduring inequalities in health to perpetuate further.

- 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, because of their high prevalence, high inequality in its 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.

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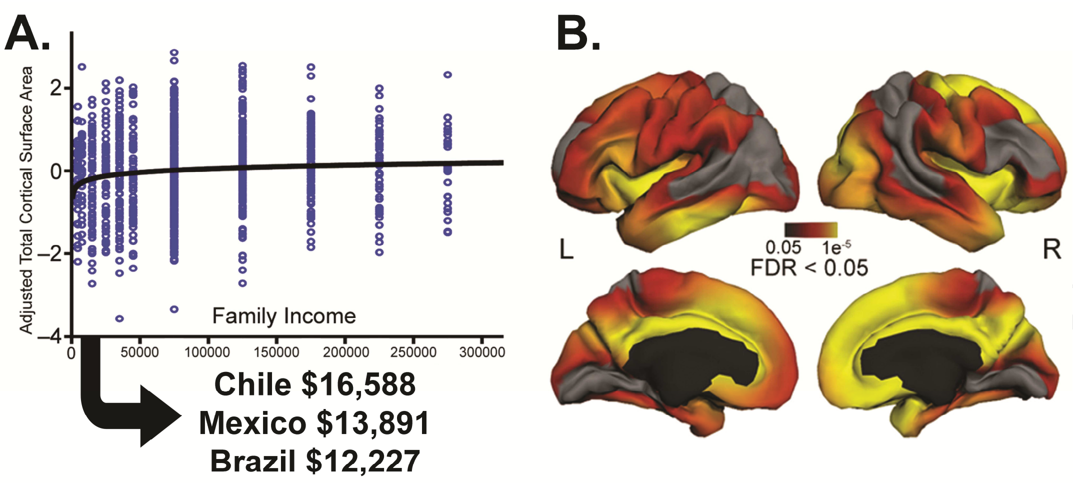
Figure Legends

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 comes from an American cohort (22), and as 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 OECD 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 figure depicting the logarithmic relationship between poverty and cortical surface (22).

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 this might mediate the effect of urbanicity. From (52). **B)** Studies looking at the brain effect of urbanicity have been done in German and Scandinavian cities, but little is known about mega-cities over 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).


A.
Adjusted Total Cortical Surface Area
2
0
−2
−4
Family Income
0
50000
100000
150000
200000
250000
300000
Chile $16,588
Mexico $13,891
Brazil $12,227
B.
L
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0.05
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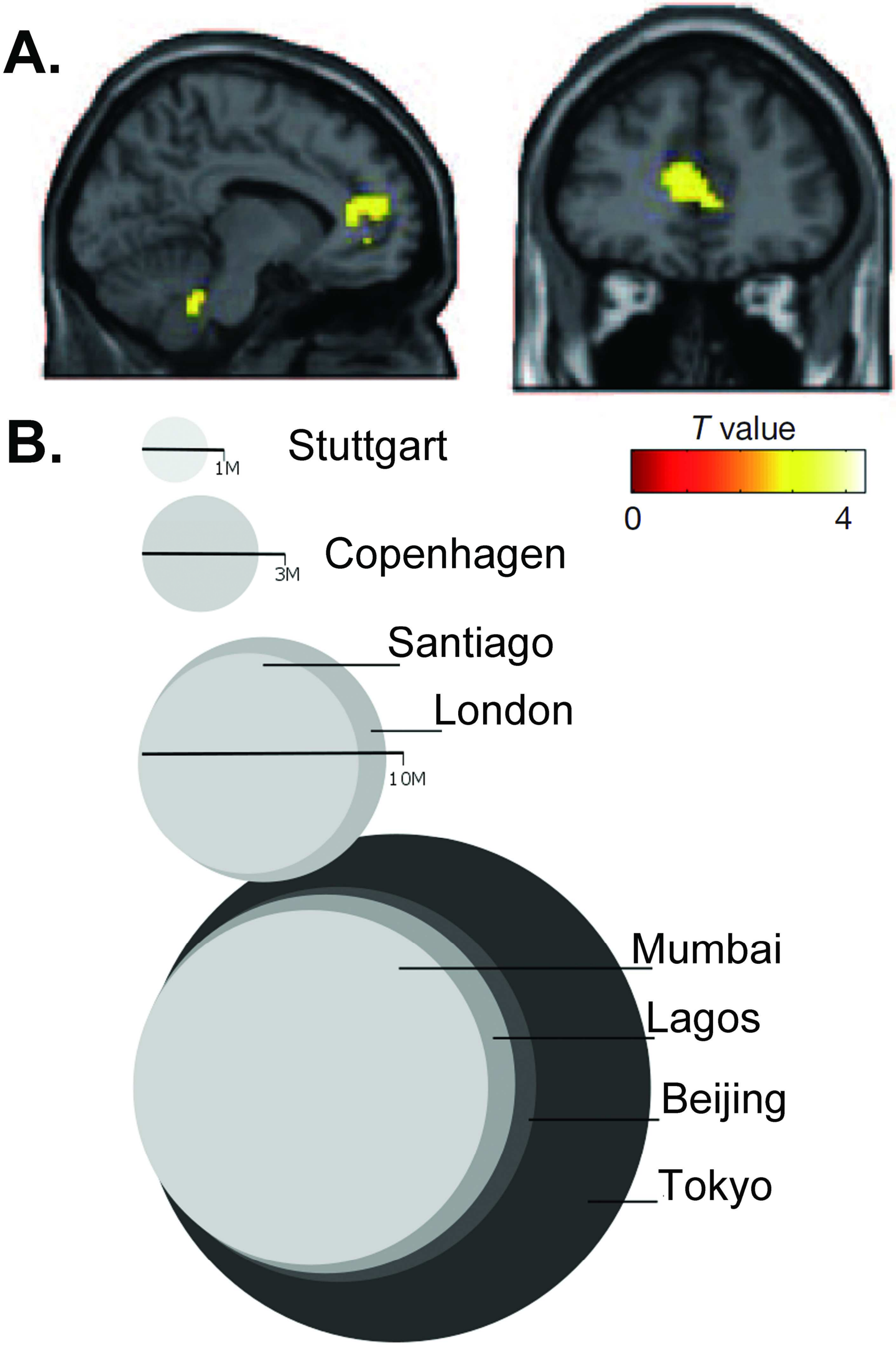
FDR < 0.05


A.
B.
Stuttgart
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