Structural brain abnormalities in schizophrenia in adverse environments: examining the effect of poverty and violence in six Latin American cities


Summary

Background
Social and environmental factors such as poverty or violence modulate the risk and course of schizophrenia. However, how they affect the brain in patients with psychosis remains unclear.

Aims
We studied how environmental factors are related to brain structure in patients with schizophrenia and controls in Latin America, where these factors are large and unequally distributed.

Method
This is a multicentre study of magnetic resonance imaging in patients with schizophrenia and controls from six Latin American cities. Total and voxel-level grey matter volumes, and their relationship with neighbourhood characteristics such as average income and homicide rates, were analysed with a general linear model.

Results
A total of 334 patients with schizophrenia and 262 controls were included. Income was differentially related to total grey matter volume in both groups ($P = 0.006$). Controls showed a positive correlation between total grey matter volume and income ($R = 0.14, P = 0.02$). Surprisingly, this relationship was not present in patients with schizophrenia ($R = -0.076, P = 0.17$). Voxel-level analysis confirmed that this interaction was widespread across the cortex. After adjusting for global brain changes, income was positively related to prefrontal cortex volumes only in controls. Conversely, the hippocampus in patients with schizophrenia, but not in controls, was relatively larger in affluent environments. There was no significant correlation between environmental violence and brain structure.

Conclusions
Our results highlight the interplay between environment, particularly poverty, and individual characteristics in psychosis. This is particularly important for harsh environments such as low- and middle-income countries, where potentially less brain vulnerability (less grey matter loss) is sufficient to become unwell in adverse (poor) environments.

Keywords
Schizophrenia; magnetic resonance imaging; grey matter; violence; poverty.

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Method

Participants

The study is part of the Latin American Network for the Study of Early Psychosis (ANDES; www.cyted.org/redes/ANDES), a consortium of research groups from six Latin American countries: Argentina, Bolivia, Brazil, Chile, Colombia and Mexico. Six imaging groups participated in this study, totalling seven different samples acquired in different scanners located in Buenos Aires, Porto Alegre, São Paulo, Santiago, Medellin and Mexico City (the latter contributing two different samples). Participants with a diagnosis of schizophrenia or schizophreniform disorder under the age of 50 years were included in the analysis, as well as healthy controls. Further site-specific details about recruitment, assessment and inclusion criteria are described in Supplementary Table 1 available at https://doi.org/10.1192/bjp.2020.143. All participants provided written informed consent to participate, and studies were approved by their local ethics committee (Buenos Aires, Bioethics Committee Fundación para la lucha contra las Enfermedades Neurológicas de la Infancia (FLENI), approval number 1612; Medellin, Bioethics Committee, School of Medicine, Universidad de Antioquia, approval number N.013; Mexico City, Ethics and Scientific Committees of the Instituto Nacional de Neurología y Neurocirugía, approval number 98/12; Porto Alegre, Ethics Committee of Hospital de Clínicas de Porto Alegre, approval number 2010-0348; Santiago, Ethics and Scientific Committee Comité Ético y Científico Ciencias de la Salud Pontificia Universidad Católica (CEC MED UC), approval number 14-442; Sao Paulo, Research Ethics Committee of Universidade Federal de São Paulo (UNIFESP), approval number 1737/06).

Environmental exposure

For each participant, we obtained a measure of exposure to environmental violence and income. As a proxy for environmental violence, we used the homicide rate reported for the area where the participant was living at the time of the study. For poverty, average household income of the neighbourhood where the participant lived, according to official open-access government data, was used. In one centre (Mexico), family income was obtained directly from the participants. As addressed later in the discussion, both characteristics are therefore about the environment where the participant was living at the time of the study, rather than the participant. Characteristics are therefore about the environment where the participant was living at the time of the study, rather than the participant’s characterisation. Table S1 details the sources of the data used. To account for differences in how the metrics were obtained, particularly when measuring income, we used standardised z-scores normalised for each participating site. The correlation between environmental violence and income was $-0.33$ ($P < 0.006$). Potential effect of this shared variance is explored further in Supplementary file 1, which shows that our main results are unchanged when considering only one of these environmental variables at the time.

Preprocessing of images

T1-weighted images were acquired in the different centres, using different scanners and protocols (see Supplementary Table 1), but were all preprocessed equally. This involved using SPM12 (www.fil.ion.ucl.ac.uk/spm/) running on MATLAB (Mathworks) for tissue segmentation, creation of a cohort-specific template with DARTEL,15 normalisation to Montreal Neurological Institute (MNI)16 and extraction of voxel-level modulated grey matter volumes. To account for differences in MRI scanners and acquisition protocols, grey matter volumes were corrected by ComBat (https://github.com/Jfortin1/ComBatHarmonization) running on MATLAB.17 Briefly, this algorithm treats the scanner effect as additive and multiplicative, assuming that the voxel-level values can be modelled as a linear combination of the biological variable and the site effects, with the error term being modulated by additional site-specific scaling factors. It uses empirical Bayes to improve the estimation of the model with small sample sizes. To explore the potential effect of ComBat on our results, a confirmatory analysis of our main result, using a mixed-model approach to deal with the inter-scan variance, is included in Supplementary file 1.

Statistical analysis

Harmonised, intersite grey matter volumes were then analysed with a single general linear model that included being a case (patients, 1; controls, −1), our two variables of interest (poverty and violence) and their interaction with case. Age and gender were included as covariates of no interest. Following the recent, large Enhancing Neuro Imaging Genetics through Meta-Analysis study,18 we looked for possible regional specificity of changes by normalising the voxel-level data by the total grey matter volume of the individual. As described in the Results, we also performed a case–control comparison between selected subgroups according to income (top 20th percentile compared with bottom 20th percentile), balanced across sites and correcting for age and gender.

Data were analysed with SPM12 (www.fil.ion.ucl.ac.uk/spm/) and custom-built scripts both running on MATLAB 2016 (Mathworks, USA, www.mathworks.com). Code is available from the authors upon request. All $P$-values are reported as significant when <0.05, corrected with false discovery rate when presenting voxel-level results.

Results

A total of 334 patients with schizophrenia and 262 healthy controls were included in the analysis. Table 1 describes the characteristics of the participants, including their demographics, clinical characteristics and exposure to environmental factors.

Grey matter volume and income

Median annual income for patients with schizophrenia and controls were $7133 and $8848, respectively, as detailed in Table 1. This corresponds to 14% and 17%, respectively, of the equivalent USA figure. There was a significant interaction between income and case in whole-brain grey matter volumes ($\beta = -563.8 + 204.3, P = 0.006$). Controls showed a positive correlation with income, which was significant when they were considered independently (Fig. 1(a); $R = 0.14, P = 0.021$). This positive correlation was not present in patients with schizophrenia. If anything, income was negatively correlated with grey matter volume in that group, albeit non-significantly (Fig. 1(b); $R = -0.076, P = 0.17$). The direction of this differential relationship of income on cases and controls was seen in sites exclusively recruiting first-episode patients (Mexico and Chile), as well as in other sites recruiting chronic patients (Supplementary Fig. 1A). It was also seen in both men and women (Supplementary Fig. 1B). As shown in Supplementary file 1, interaction analyses exploring whether this differential relationship varied according to chronicity or gender were not significant. Furthermore, the direction of the relationship between income and total grey matter volume was consistent across the participating sites (Supplementary Fig. 2), albeit not always significant considering the smaller sample size.

Exploring the relationship between income and grey matter volume at the voxel level (correcting for multiple comparisons) highlighted that the significant interaction between income and...
case was distributed across the whole cortex (Fig. 1(c)). All significant voxels showed the same direction of the interaction, showing a positive correlation with income for healthy controls and a negative correlation for patients with schizophrenia. We then explored how specific brain regions were related to income after accounting for changes in whole-brain grey matter. An initial pattern emerged of voxels located in the prefrontal region showing a negative interaction between case status and income after accounting for total grey matter volumes (Fig. 2(a)). In this region, income was positively related with higher grey matter volume in healthy controls (coded 1 in our model), with the correlation being stronger than the one observed in the rest of the brain. In patients with schizophrenia (coded 1 in our model), this region behaved like the rest of the brain (Fig. 2(b)). The second pattern observed was a positive interaction between grey matter volume and case status in the right hippocampus, as well as a few voxels in the frontal insula and putamen (Fig. 2(c)). In these regions, patients with schizophrenia showed a positive correlation with income, after accounting for global brain changes, whereas healthy controls showed a negative correlation (Fig. 2(d)).

The observed relationship between income and grey matter volume implied that case–control differences varied according to whether the sample was obtained from high earners or low earners. Figure 3(a) shows the case–control comparison of 63 patients with schizophrenia and 55 controls who were within the top 20th percentile for household income from all the included cities, with widespread significant differences (all volume reductions observed in patients with schizophrenia) echoing results from a recent large case–control study.18 Figure 3(b) shows the same analysis performed with the same number of participants, but from the bottom 20th percentile for household income. Differences are only restricted to a few areas (bilateral insula, hippocampi, superior temporal regions and prefrontal cortex).

**Grey matter volume and environmental violence**

As described in Table 1, participants were exposed to high levels of environmental violence, living in areas with median rates of homicides per year per 100,000 inhabitants, respectively. This is equivalent to 2.5–3 times the rate reported for all of Europe. The relationship between environmental violence and total grey matter volume, as well as its interaction between case and violence, were not significant. Voxel-level analyses did not find any significant results. There was a trend toward a significant interaction between environmental violence and total grey matter volume (P = 0.064), with a decrease in grey matter volume in more violent environments observed only in patients with schizophrenia (Supplementary Fig. 3).

**Discussion**

Environmental and social factors are known risk factors for schizophrenia, as well as modulators of its course. Previous literature showed that these factors are associated with differences in brain structure in healthy individuals, but how they are related in patients with psychosis is still unclear. We used a relatively large sample of patients with schizophrenia living in Latin American cities to explore the structural brain correlates of living among these factors, taking advantage of the large and unequal distribution of the exposure in these populations. We found a significant relationship between income and grey matter volume: controls presented with larger total grey matter volume when living in areas with higher household incomes, but this relationship was not present...
in patients with schizophrenia. As such, structural brain differences in schizophrenia and healthy controls vary according to the environment the individual lives in, possibly reflecting different neuro-pathological mechanisms.

Lower income has been previously related to lower global grey matter in healthy individuals, but this relationship was limited to the poorest households. Considering the average income of our participants, it is not surprising to observe such a relationship across our sample of healthy controls because most of them lived in similar conditions to the most deprived participants in those studies of high-income countries. As has been discussed in the literature, it is likely that this effect is multifactorial; it might be related to better perinatal care, better nutrition and lower risk of infections at an early age, less exposure to toxic substances, better access to education and even less stress in those not exposed to poverty. It is remarkable that despite looking at the characteristics of the environment where participants were living and not their own personal exposure to poverty, we still see a significant effect. Individuals living in a poor environment are not necessarily exposed to the same state of deprivation; they could even have moved to that neighbourhood recently. Latin American cities tend to be highly segregated according to socioeconomic class, which increases the precision of this estimate. It might also be that the level of poverty in Latin American cities is such that the relationship is significant even when using a noisy proxy measure that might dilute its effect. On the other hand, epidemiological studies have suggested that environmental poverty has an effect even after accounting for personal experience of poverty. We might be visualising a real environmental effect rather than just a supposed proxy.

We initially hypothesised that the observed positive association between income and grey matter volume in healthy individuals would be stronger in patients with schizophrenia because we expected poverty as an adverse factor to have a bigger effect on a vulnerable brain already affected by psychosis. Surprisingly, this relationship was not present in patients with schizophrenia. This might be because of higher-income patients presenting with neurodevelopmental abnormalities that prevent them from benefiting from the environment. However, socioeconomic gradients in a variety of measures have been observed in patients with schizophrenia with other neurodevelopmental disorders. An alternative explanation could be that developing schizophrenia is the result of an underlying biological vulnerability interacting with an adverse environment: perhaps less grey matter damage (a proxy for biological vulnerability) is needed to develop a psychotic episode in a very poor (adverse) environment. Similarly, the disorder would only emerge when the grey matter damage (brain vulnerability) is such that the enriched environment cannot contain it. The anatomy of schizophrenia is not an independent process detached from the environment, but rather is inseparable from it. Conceptually, schizophrenia becomes inseparable from the ecological niche in which it presents.

The observed relationship with income was mostly a global whole-brain effect. However, further examination of this effect after accounting for the global changes showed interesting localised results. The prefrontal cortex seems to be a region that benefits highly from a more affluent environment in healthy individuals, but not in patients with schizophrenia. The association in the prefrontal cortex is in line with the cognitive profiles most related to income, particularly executive functions. This does not mean that a more affluent environment has no effect on patients with schizophrenia because, after accounting for the global effect, patients showed a significant correlation with income in right hippocampal volume. The hippocampus has been highlighted as a critical region in the neuropathology of schizophrenia. However, it is

Fig. 1 Total grey matter volumes are differentially related to income in patients with schizophrenia and controls. Relationship between income and total grey matter volumes in (a) controls and (b) patients with schizophrenia (note the different direction of the relationship). (c) Voxel-level analysis of the relationship between income and grey matter volume showing that the significant interaction was widespread across the cortex (t-values from highlighted voxels are significant at *P* < 0.05 corrected with false discovery rate).
also interesting to note that plastic hippocampal volume changes have been observed with other interventions in patients with schizophrenia, such as exercise, suggesting that the hippocampus is a target of both schizophrenia neuropathology and a favourable environment.

The brain in patients with schizophrenia in the lower-income group was more similar to that of healthy controls than in the upper-income group. This has several implications. These differences should be considered using the multivariate approaches under development that use statistical learning methods on neuroimaging data, particularly when including populations exposed to different environments. If these environmental factors are not accounted for, algorithms developed with data from higher-income countries will only be useful for the few wealthy people in lower-income countries who have similar living standards, further increasing existing inequalities. Our findings also support a new hypothesis to explain the alleged better prognosis of patients with schizophrenia in low- and middle-income countries who have similar living standards, further increasing existing inequalities. Our findings also support a new hypothesis to explain the alleged better prognosis of patients with schizophrenia in low- and middle-income countries who have similar living standards, further increasing existing inequalities. Our findings also support a new hypothesis to explain the alleged better prognosis of patients with schizophrenia in low- and middle-income countries who have similar living standards, further increasing existing inequalities. Our findings also support a new hypothesis to explain the alleged better prognosis of patients with schizophrenia in low- and middle-income countries who have similar living standards, further increasing existing inequalities.

There was also an interesting interaction between environmental violence and case that did not reach statistical significance. Patients with schizophrenia appeared more vulnerable to a violent environment, showing reduced total grey matter. It has been proposed that exposure to deprivation and violence have different neurodevelopmental effects. Our differential results of poverty and environmental violence would fit well with this framework.

Future studies will need to explore further the effect of environmental violence on the brain.

There are several limitations to our study. As discussed above, we characterised the environment where the participant was living, rather than assess the personal exposure to violence or poverty. Furthermore, environmental exposure (where participants lived) was obtained at the time of scanning, not considering the existence of critical periods in their exposure. Future studies might be able to address whether the observed effect of poverty depends on personal or environmental poverty, or the exposure at a specific period of life, such as childhood. Our study also included patients with schizophrenia of a wide range of ages and at different stages of the disorder. Chronicity and medication are known to have effects on brain morphology. However, we also showed that results...
were consistent across sites, and this heterogeneity in our participants also increased the generalisability of our findings. Environmental measures were not orthogonal to each other either. We preferred using these metrics than the new composite variable, for ease of interpretation. As described in Supplementary file 1, we also explored the effect of analysing only one environmental parameter at a time in our linear model, with similar results. Our environmental metrics were also heterogeneous (particularly metrics looking at income), and our normalisation procedure allowed us to examine relative rather than absolute differences. Nonetheless, our study shows original data of a population living in an unequally distributed adverse environment such as Latin America, which has been poorly represented in the literature. Taking advantage of its highly contrasting living conditions, our study provides novel evidence about the environment effect on the neurobiological bases of schizophrenia.

**Fig. 3** Case-control analysis for the wealthiest and poorest households. Decreases in grey matter volume in 66 patients with schizophrenia compared with 53 controls, corresponding to (a) the top 20th percentile and (b) bottom 20th percentile for household income across the sample. Patients with schizophrenia did not show any areas that were larger than healthy controls in either comparison. Results are balanced for the different centres and controlled for gender and age. Highlighted voxels are significant at P < 0.05 corrected with false discovery rate, and colour-coded according to the t-value. Note the widespread differences in more affluent settings, and the more restricted differences in the poorest households.

**Supplementary material**

Supplementary material for this article are available online at http://doi.org/10.1192/bjp.2020.143

**Data availability**

The data that support the findings of this study are available from the corresponding author (N.A.C.), subject to permission from the senior author of each site (N.A.C., R.A.B., C.F.-S., L.F.S., R.N., A.H.B., and D.E.L.-J.), upon reasonable request.

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**Author contributions**

leakage and secured funding for data acquisition in their respective centres. N.A.C., A.Z., F.R.-M., L.S.C., M.N.C., A.M.-Z., J.U., C.L.-J., S.M.G., C.S.G., C.F.-S. and R.A.B. wrote the manuscript. All authors contributed to data acquisition, and critically reviewed and approved the finalised manuscript. N.A.C. had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Declaration of interest

C.F.-S. has served as a consultant for Janssen, and F.R.-M. has served as a speaker for Pfizer, personal fees from Sanofi-Aventis and personal fees from Torrent, outside the submitted work. The other authors report no biomedical financial interests or potential conflicts of interest.

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