



ORIGINAL ARTICLE

Megacities, migration and an evolutionary approach to bipolar disorder: a study of Sardinian immigrants in Latin America

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Objective: To determine whether people with a Sardinian genetic background who live in the megacities of South America have a higher frequency of hypomania than residents of Sardinia.

Methods: A community survey of Sardinian immigrants was carried out in four Brazilian metropolises (n=218) and Buenos Aires (n=306). The results were compared with those of a study involving a similar methodology (Mood Disorder Questionnaire [MDQ] as a screening tool) conducted in seven Italian regions, including a sub-sample from Sardinia.

Results: There was a higher prevalence of lifetime hypomania among Sardinians living in the Brazilian metropolises than among those living in Sardinia. This result was also consistent with Sardinian immigrants in Buenos Aires. After stratification by sex and age, the lifetime prevalence of MDQ scores ≥ 8 among Sardinians in South-American megacities and Sardinia was 8.6% vs. 2.9%, respectively ($p < 0.0001$).

Conclusions: The higher frequency of hypomania in migrant populations appears to favor an evolutionary view in which mood disorders may be a maladaptive aspect of a genetic background with adaptive characteristics.

Keywords: Bipolar disorder; migration; evolutionary approach; megacities; Latin America

Introduction

In the early 1950s, 30% of the world's population lived in cities; by 2050 this number will have reached 66%.¹ The lifestyles of people moving from rural areas to megacities may change due to the impact of noise, overpopulation and light pollution, which accelerate circadian biorhythms.²⁻⁶

It has been hypothesized that having a hyperthymic temperament or even a sub-threshold bipolar mood profile may have an adaptive role in helping people cope with this new "fast-paced lifestyle." Moreover, it has also been suggested that the inhabitants of metropolises may suffer higher rates of bipolar disorder (BD).^{7,8}

Based on this hypothesis, it may be of interest to verify whether people living in megacities show higher rates of bipolar spectrum profiles, including sub-threshold cases of BD, than people with the same genetic background living in their region of origin.

Studying immigration from the Italian region of Sardinia may offer several advantages: a) the Sardinian population is one of the most genetically stable and homogeneous in the world⁹; and b) urban areas in Sardinia never exceed 150,000 inhabitants; migrants mainly originate from inland rural areas.¹⁰ A preliminary study appeared to confirm a higher rate of hypomania in a sample of Sardinian immigrants residing in the city of Buenos Aires, Argentina.¹¹

The purpose of the present study was to measure the hypomania rate in a sample of Sardinian immigrants in four Brazilian metropolises (Curitiba, Belo Horizonte, Rio de Janeiro and São Paulo) using the Mood Disorder Questionnaire (MDQ).¹² The rates in Brazil were compared to those found in Buenos Aires and seven Italian regions, including Sardinia.

As defined by the United Nations Department of Economic and Social Affairs, a megacity has more than 10 million residents.¹³ According to this definition, São Paulo,

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Buenos Aires and Rio de Janeiro are megacities. Another definition by the World Bank stipulates a total population in the millions and a population density of 2,000 inhabitants per square kilometer.¹⁴ According to the latter definition, Belo Horizonte and Curitiba also classify.

Although the MDQ is not the most accurate means of identifying BD cases, it was chosen for this study on the basis of our previous research^{15,16} which verified that people with positive MDQ scores show a bipolar profile, which includes subthreshold cases of BD.¹⁵

Methods

Design and setting

The study is based on a community survey of Sardinian immigrants in the aforementioned Brazilian metropolises conducted between November 2017 and March 2018. The results were compared with those of an epidemiological survey carried out in seven Italian regions (Agenzia Italiana del Farmaco [AIFA] study on the use of antidepressants),¹⁷ including its sub-sample of Sardinian residents, as well as with results from Buenos Aires.^{10,11} These studies used a similar methodology.^{10,11,17,18}

Sample

Both men and women over 18 years of age were included in the survey. Associations of Sardinians provided a list of immigrant families in Brazil. All individuals on the list were contacted. The sample included first and second generation Sardinian immigrants (children with two Sardinian parents).

Tools

Demographic information (sex, age, residence, education, first or second generation) was collected using a structured tool. Hypomania was screened using validated Italian,¹⁹ Brazilian Portuguese²⁰ and Argentinian Spanish²¹ versions of the MDQ. Interviews were conducted by phone. The interviewers, native speakers of Italian with a good knowledge of Spanish or Portuguese, were psychiatric rehabilitation technicians or trained physicians. The cutoff for MDQ positivity was set at ≥ 8 'yes' scores, as in the previous Argentinian study,¹¹ the Italian study used for comparison^{17,19} and the Brazilian validation study.²⁰

Statistical analysis

Statistical analysis involved comparing MDQ scores (the dependent variable) and independent variables (gender, age, residence, and generation) with a direct standardization method. The analysis was conducted by comparing the Brazilian immigrant sample to each of the other three samples, which were standardized according to gender and age as a category (\geq or $<$ 40 years). We created four strata by gender and age (\leq or $>$ 40 years) and recalculated the prevalence rates by balancing the dimensions of the two groups according to the dimensions in

each specific stratum, based on the following definition of standardization: "Two rates can be compared without bias if they are adjusted so as to equalize to weight given by another factor that could be related to outcome. This process, called standardization, shows what the overall rate would be if strata-specific rates were applied to a population made up of similar proportion of people in each stratum."²²

Statistical significance was calculated with a χ^2 test (1 degree of freedom). The measures are expressed as odds ratios (OR) with 95% confidence intervals (95%CI) and were calculated using Miettinen's simplified method.²³

Ethical aspects

Interviewers informed the participants about the nature and purpose of the study and the option to terminate the interview at any time. Participants were asked to provide informed oral consent (by phone). The participants were given information about data protection and privacy laws. The interviewers explained that the data collected would be used in an anonymous database and that their confidentiality would be maintained in accordance with Brazilian and Italian data protection laws. The study was conducted in accordance with the ethical principles of the Helsinki Declaration. The ethics committee of Azienda Ospedaliero Universitaria di Cagliari, Cagliari, Italy, as well as the board of the Universidad del Museo Social Argentino and Universidade Federal do Rio de Janeiro, approved the final study protocol.

Results

The sample consisted of 218 individuals of Sardinian origin who were first- or second-generation immigrants and current residents of four Brazilian megacities: São Paulo, Rio de Janeiro, Belo Horizonte or Curitiba.

A total of 291 individuals were selected from the lists provided by the Brazilian Sardinian immigrant associations: 73 (25.1%) did not participate because they either could not be found (49, 16.8%) or refused to participate (24, 8.2%). Table 1 shows the Brazilian sample's demographic characteristics in comparison with the other samples.

Table 1 shows that the sample of Brazilian immigrants did not differ significantly from the Argentinian or Sardinian samples regarding gender, although there were significantly more males than in the Italian sample.¹¹

The Brazilian immigrants were also similar in age to the Argentinians, but there were fewer people ≤ 40 than in the Sardinian and Italian samples. Moreover, the education level of the Brazilian immigrants was higher than the other three control samples, and the Argentinian sample had a higher education level than the Italian and Sardinian samples.¹¹

Table 2 shows the lifetime prevalence of MDQ scores ≥ 8 in Sardinian immigrants in Brazil compared to those in Buenos Aires, Sardinia, and Italians from seven different regions.¹⁷ Comparisons with the latter two samples were made after direct standardization according to sex and age (\leq or $>$ 40 years) due to the high heterogeneity level of

Table 1 Demographic characteristics of Sardinian immigrants in Brazil and Argentina compared to populations from Italy and Sardinia

	Sardinians in Brazil (n=218)	Sardinians in Argentina (n=306)	AIFA study Sardinian sample (n=309)	AIFA study Italian overall sample (n=3,398)
Males (%)	52.3	47.7 ($\chi^2 = 1.07$, p = 0.30)	47.8 ($\chi^2 = 0.98$, p = 0.32)	42.3 ($\chi^2 = 8.37$, p = 0.004)
Age \leq 40 years (%)	20.2	14.5 ($\chi^2 = 3.07$, p = 0.08)	37.9 ($\chi^2 = 18.83$, p < 0.001)	43.4 ($\chi^2 = 27.65$, p < 0.001)
Graduate-level education (%)	53.2	38.6 ($\chi^2 = 11.4$, p < 0.001)	24.6 ($\chi^2 = 12.20$, p < 0.001)	26.2 ($\chi^2 = 20.21$, p < 0.001)

Data presented as %.

AIFA = Agenzia Italiana del Farmaco.

All comparisons are based on one degree of freedom.

Table 2 Lifetime prevalence of Mood Disorder Questionnaire (MDQ) scores in Sardinian immigrants to Brazil and Argentina compared to populations from Italy and Sardinia (Agenzia Italiana del Farmaco [AIFA] study)

Sardinians in Brazil n (%)	Sardinians in Argentina n (%)	Sardinian sample n (%)	Italian sample n (%)	OR (95%CI)	χ^2	p-value
20.0 (9.2)	22.0 (8.9)			1.30 (0.66-2.56)	0.68	0.41
16.1 (7.4)*		9.0 (2.9)		2.66 (1.81-6.64)	5.63	0.02
17.80 (8.0) [†]			10.3 (3.0)	2.78 (1.58-4.83)	15.6	< 0.0001

95%CI = 95% confidence interval; OR = odds ratio.

* After direct standardization by sex and age ("Sardinians in Brazil" sample standardized according to the "Sardinian sample").

[†] After direct standardization by sex and age ("Sardinians in Brazil" sample standardized according to the "Italian sample").**Table 3** Lifetime prevalence of Mood Disorder Questionnaire (MDQ) scores \geq 8 in Sardinian immigrants in South American Metropolises (Brazil and Argentina) vs. Sardinians in Sardinia and seven other regions of Italy (Agenzia Italiana del Farmaco [AIFA] study database)

Age and gender	Sardinians in South America n (%)	Sardinians in Sardinia n (%)	Italians n (%)	Comparison with Sardinian residents			Comparison with Italians		
				OR (95%CI)	χ^2	p-value	OR (95%CI)	χ^2	p-value
\leq 40 males	5 (8.9)	1 (2.2)	25 (3.7)	4.41 (0.47-103)	2.08*	0.15	2.55 (0.81-7.41)	2.39	0.120
\leq 40 females	6 (10.5)	3 (4.2)	28 (3.4)	2.66 (0.60-13.3)	2.10*	0.15	3.34 (1.34-8.04)	9.18	0.002
> 40 males	11 (5.4)	2 (1.9)	24 (3.1)	2.95 (0.60-19.7)	2.14	0.15	2.43 (1.10-5.24)	6.20	0.15
> 40 females	20 (10.6)	3 (3.3)	26 (2.3)	3.47 (0.82-15.1)	4.32	0.04	5.02 (2.63-9.57)	33.0	< 0.0001
All males	16 (6.2)	3 (2.0)	49 (3.4)	3.22 (0.86-14.2)	3.74	0.05	1.88 (1.01-3.47)	4.70	0.03
All females	26 (10.5)	6 (3.7)	54 (2.8)	2.83 (1.08-7.84)	5.40	0.02	3.93 (2.34-6.56)	34.9	< 0.0001
All \leq 40	11 (8.3)	4 (3.5)	53 (3.5)	2.54 (0.72-9.79)	2.59	0.11	2.48 (1.19-5.06)	7.41	0.006
All > 40	31 (7.9)	5 (2.6)	50 (2.6)	3.24 (1.18-9.67)	6.39	0.01	31.8 (1.95-5.17)	26.6	< 0.0001
Total	42 (8.0)	9 (2.9)	103 (3.0)	3.69 (1.70-8.21)	8.80	0.003	2.90 (1.34-6.50)	36.4	< 0.0001
Total (standardized) [†]	47.2 (9.0)	-	103 (3.0)				3.17 (2.18-4.60)	44.2	< 0.0001
Total (standardized) [‡]	45.1 (8.6)	9 (2.9)		3.14 (1.46-7.01)	10.4	0.001			

95%CI = 95% confidence interval; OR = odds ratio.

Data presented as n (%).

* With Yates' correction.

[†] After direct standardization by sex and age ("Sardinians in Brazil" sample standardized according to the "Italian sample").[‡] After direct standardization by sex and age ("Sardinians in Brazil" sample standardized according to the "Sardinian sample").

the samples. The standardized frequencies in Brazilian immigrants were higher than those in Sardinia and Italy and similar to those of Buenos Aires.

Table 3 compares the Sardinian immigrants in the five metropolises of Argentina and Brazil with the two samples of Sardinians residing in Sardinia and seven other regions of Italy. The frequency of MDQ scores \geq 8 among Sardinian immigrants in the South American megacities was higher than that among Sardinians in Sardinia, after stratification by sex and age: 8.6% vs. 2.9% ($\chi^2 = 44.16$, 1 df; p < 0.001; OR = 3.17; 95%CI 2.18-4.60). These differences (i.e. higher prevalences in immigrants) reached statistical significance in subgroups of women,

men, women \leq 40 years of age, and women > 40 years of age.

The Sardinian immigrants in the South American metropolises had a higher frequency of MDQ scores \geq 8 than the total sample of Italians after stratification by sex and age: 9% vs. 3% ($\chi^2 = 44.16$, 1 df; p < 0.001; OR = 3.17; 95%CI 2.18-4.60).

The prevalence differences were also significant in the subgroups subdivided by age or gender. However, when subdivided by both age and gender, the higher prevalence among male immigrants \leq 40 and > 40 years of age never reached statistical significance, although it did in the two subgroups of women.

Although the frequency of MDQ scores ≥ 8 in first-generation immigrants was lower than in the second generation (5% vs. 10%), it was not significant (χ^2 with Yates = 0.48; $p = 0.462$; OR = 0.48; 95%CI 0.02-3.64). However, this finding agrees with the previous results collected in Buenos Aires (a 5% difference between Sardinian immigrants in Brazil and Sardinians in Sardinia, vs. an 8% difference between Sardinian immigrants in Buenos Aires and Sardinians in Sardinia), and the first generation prevalence is homogeneous between the two groups of immigrants in Brazil and Argentina (χ^2 Yates Corrected = 0.207; $p = 0.649$ OR = could not be calculated). Thus, if we consider the entire number of Sardinian immigrants in the megacities, the trend emerging in the Argentine sample is confirmed, which indicates a risk in the second generation of immigrants. (1.5% in first-generation immigrants vs 9.0% in the second generation, $\chi^2 = 4.54$; $p = 0.033$; OR = 6.61; 95%CI 1.01-121.6).

Discussion

According to the results of this study, there is a higher prevalence of lifetime hypomania among Sardinian immigrants in four Brazilian metropolises than among residents of Sardinia. This finding confirms previous results in a sample of Sardinian immigrants in Argentina.¹¹

The two studies conducted in Buenos Aires and Brazil appear to converge in providing evidence of a higher rate of lifetime hypomania both in Sardinians who migrated from rural areas in the 1960s and their children who currently live in South-American megacities.

There was a trend in both the Argentinian and Brazilian studies towards a higher frequency of hypomania among second-generation immigrants than first-generation immigrants. Although this trend was homogeneous, it was significantly different only in the Argentine sample and the pooled sample, even though the high agreement in the trend suggests that the non-significant difference in the Brazilian sample was due to the sample size and to the low study power.

However, this must be compared with the fact that first-generation immigrants are an older population than second-generation immigrants. Indeed, even in the comparative population in the Italian AIFA study, participants over 65 had a significantly lower lifetime rate (i.e., about three times lower) of positive MDQ than younger people.²⁴ Older people (in Italy and Brazil) have lower rates of MDQ. Although first-generation immigrants to Brazil have lower MDQ rates, the fact that they are also older than second-generation immigrants means we cannot say that belonging to the first generation of migrants represents either a risk factor or a confounding factor. Thus, the results prevent us from determining whether there is greater vulnerability among second-generation immigrants, given that the increasing age-dependent frequency could be considered confounding factor.

Nevertheless, this is noteworthy. This comparison of cross-sectional population studies with small samples based on screening tools can only generate hypotheses that must be verified by studies with more appropriate methodologies.

It should be pointed out that:

- 1) In concert with the study hypothesis, a bipolar diathesis could be "diluted" in second-generation immigrants. If this were the case, we would expect a lower rate in the second generation. However, our sample consisted of only second-generation immigrants whose parents are both Sardinian, thus such a dilution effect could be ineffective;
- 2) Environmental factors (in the context of megacities) could amplify the effects of genetic selection;
- 3) Considering that these are lifetime frequency rates, a recollection bias may have influenced the low frequency in the elderly population, both in the Sardinians living in Sardinia and the immigrant population (in which even the second-generation immigrants are mainly elderly).

It has been hypothesized that migration, especially when not imposed by external factors such as war, may select more explorative and novelty seeking people, such that a higher rate of hypomania could be the consequence of a selection based on temperament.^{8,10,25}

It could also be that the biological rhythms imposed by megacities favor episodes of hypomania; in fact, noise and light pollution, shorter meals, less time to relax, greater exposure to legitimate and illicit stimulants are factors that by themselves can induce hypomania or raise the prevalence of the phenomenon.²⁻⁶ This environmental perspective does not necessarily contrast with genetic drift.²⁶ On the contrary, we cannot deny that people with a hyperthymic temperament may adapt better to a new world, since such a world may attract people able to adapt to it. Thus, it has been proposed that these increased rates of hypomania or sub-threshold bipolar disorders may be due to the natural selection of people with hyperactive behavior.^{7,8} In addition, the new social conditions, including higher levels of competition and changes in circadian rhythms, may result in a synergistic and neo-pathoplastic effect of the two factors.

Genetic drift might explain these results, since it can characterize explorative behavior and the drive to seek novelty by leaving the homeland. Environmental factors may add to genetic predisposition, since they can affect biological rhythms and may contribute to a greater risk of bipolar disorder. The two factors could work together, since explorative behavior is a stimulus to go to livelier places or construct places with a more accelerated lifestyle.

These hypotheses will be better verified with the advent of a more accurate screening method for studying risk and resilience factors. It would be important to determine whether there is a common genetic background for increased explorative behavior and a risk of developing bipolar disorders. It would also be of interest to perform genetic testing to identify subgroups of populations with adaptive temperaments vs. those without a bipolar disorder. It is likely that individuals without a bipolar disorder adjust better to everyday life and that individuals with hyperthymic or cyclothymic temperaments could have an advantage over those with other temperaments.

In terms of limitations, the sample size was small when testing differences according to subgroup, even in the

additional analysis with the Argentinian sample. Another important limitation was using MDQ scores to identify a diagnostic group (“sub-threshold bipolar disorders”), which is hard to define with reliable criteria and about which there is much controversy. This is partly due to the innovative value of the hypotheses and the fact that, as a consequence, the methodologies will have to be improved. Thus, the results of this study can be considered of heuristic and hypothesis-generating value.

In conclusion, in a sample of Sardinian immigrants from four Brazilian metropolises, the present study confirmed a higher prevalence of lifetime hypomania than in residents of Sardinia. Such a phenomenon had previously been suggested in a sample of Sardinian immigrants in Argentina.

It is impossible to say whether this difference is attributable to the pre-selection of hyperthymic individuals due to the migratory process or to megacities, which, with their accelerated rhythms and dysregulation of bio-rhythms, favor higher rates of hypomania. However, in this field, theories of genetic evolution and social drift are not necessarily incompatible and may be complementary. In other words, people with explorative traits may build habitats that accommodate accelerated rhythms to which others with similar traits may be attracted.

At present, we can only confirm that the higher frequency of hypomanic features identified in immigrant populations appears to favor an evolutionary view in which mood disorders may be the maladaptive side of an underlying (genetic) adaptation.

An evolutionary view of bipolar disorder may also have implications for the stigma associated with this disorder. If it were confirmed that genetic features associated with BD have an adaptive advantage, the self-evaluation of those affected by a “hereditary disorder” and others could change, perhaps leading to a decrease in discrimination and stigmatization.

Disclosure

The authors report no conflicts of interest.

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