

Evidence of a latitudinal gradient in the age at onset of schizophrenia

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Abstract

Variation in the age at onset of a multifactorial disease often reflects variation in cause. Here we show a linear latitudinal gradient in the mean age at onset of schizophrenia in 13 northern hemisphere cities, ranging from 25 years old in Cali, Columbia (at 4° north) to 35 years old in Moscow, Russia (at 56° north). To our knowledge, this striking association has not been previously reported. We consider several explanations, including the effects of pathogen stress, natural selection, sexual selection, migration, life-history profiles, or some combination of these factors, and we propose a test of competing causal hypotheses.

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1. Background

Schizophrenia strikes about 1% of people worldwide, producing delusions, hallucinations, disorganized speech, bizarre behavior, and emotional blunting. Typically beginning in adolescence or early adulthood, it often leads to social isolation and severe lifelong disability. Though schizophrenia is moderately heritable (Cardno et al., 1999), no susceptibility genes of major effect have been clearly replicated (McDonald and Murphy, 2003). Its pathophysiology is poorly understood (Thaker and Carpenter, 2001), and treatment is far from satisfactory (Carpenter, 2005).

Variation in age at onset is a potential clue to the causes of schizophrenia because factors that increase the risk of developing a multifactorial disease usually hasten

onset, and earlier onset usually predicts more severe disease (Childs and Scriver, 1986). Both relationships are true for schizophrenia. For example, male sex, unmarried status, poor premorbid functioning, a family history of mental illness, birth complications and urban residence have all been associated both earlier onset and more severe illness (Jablensky, 2000). However, the mechanisms by which these factors increase risk remain unknown despite extensive research.

It is generally assumed that schizophrenia interferes with the social functioning required for marriage and that the effect would be stronger among those with earlier onset and more severe illness. This would account for the 15% to 73% reduction in marriage rates among those with schizophrenia (Haverkamp et al., 1982) as well as the associations among marital status, disease risk and age at onset. However, one analysis of a large prospective data set has challenged those assumptions and suggested that marriage may protect against the illness (Jablensky and Cole, 1997). Examining the data in that report, we noticed

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another effect—those living in cities closer to the equator developed the illness earlier. Here we describe that latitudinal gradient and discuss several possible explanations, including the effects of pathogen stress, natural selection, sexual selection, migration, life-history profiles, or some combination of these factors. In addition, we propose a test of competing causal hypotheses.

2. Methods

The report by [Jablensky and Cole \(1997\)](#) listed age at onset of schizophrenia (AAO) in thirteen northern hemisphere cities. Subjects were 1431 individuals with recent-onset schizophrenia making their first treatment contact. AAO was defined as the age at first psychotic symptom and was covariance adjusted for sex, marital status, premorbid personality traits and family history of mental illness. The original source of the data was the World Health Organization Collaborative Study of the Determinants of Outcome of Severe Mental Disorders conducted between 1976 and 1985 ([Jablensky et al., 1992](#)). In each city, investigators continuously monitored all helping agencies that were the likely first points of contact for individuals with schizophrenia. Participants were examined with a set of standardized instruments and reliability was tested and maintained by conducting joint interviews and by rating audio and video-taped interviews across sites. During the interview with the patient or informant, investigators explored and dated the occurrence of 25 early symptoms and signs of the disorder. The investigator's estimate of the age at which each symptom first appeared had to be supported by a narrative summary of the early symptoms and signs, mode of onset, the progression of symptoms and any relevant circumstances.

We obtained the latitude of each city from standard references.

3. Results

The positive linear relationship between AAO and latitude is statistically significant and explains most of the variability of the data ($t=6.43$, $df=11$, $p<0.0001$, $R^2=0.790$). Although the six cities in the middle of the latitude distribution lie below the regression line, a test for nonlinearity was not significant, $t=2.02$, $df=10$, $p=0.071$, nor was the Wald-Wolfowitz runs test ($z=-0.71$, $p=0.24$). These results suggest that a linear relationship is sufficient to describe the relationship between AAO and distance from the equator.

Earlier AAO closer to the equator, however, might be simply an artifact of higher mortality closer to the equator

([Teriokhin et al., 2004](#)), because a higher proportion of those destined to developed schizophrenia later in life would have died before disease onset. Median age of the entire population in each of the 10 countries containing the 13 cities (“[The World Factbook](#),” Accessed March, 2006) correlated significantly with both AAO ($r=0.69$) and latitude ($r=0.79$), and latitude correlated significantly with AAO ($r=0.89$). Partial correlations indicate that the direct path from latitude to AAO is unaffected by controlling for median age (latitude and AAO controlling for median age: $r=0.79$; latitude and median age controlling for AAO: $r=0.48$; median age and AAO controlling for latitude: $r=-0.07$).

We also created a correlation matrix ($N=10$ countries) with the correlation structure described above and tested two path models using structural equation modeling. For the path in which latitude influences median age which then influences AAO, lack-of-fit $\chi^2=8.34$ ($p=0.004$) and goodness of fit index=0.71. For the path in which latitude influences both median age and AAO directly, lack-of-fit $\chi^2=0.02$ ($p=0.89$) and goodness of fit index=0.999. Thus, the model in which latitude influences both of the other variables directly fits very well, while the alternative fits poorly and is statistically rejected. These results suggest that the latitudinal gradient in AAO is not an artifact of a latitudinal gradient in the age structure of the populations from which the subjects were drawn.

4. Discussion

These results suggest that a factor that varies with latitude influences AAO. There are many possibilities for that factor and for the mechanism by which it influences AAO. The factor could be physical or biological, act on individuals or evolution and influence disease risk or the maturation of a trait related to schizophrenia.

One possibility is that the factor is a known correlate of AAO. However, four are unrelated to the gradient, because in the report from which our data were drawn ([Jablensky and Cole, 1997](#)), AAO was statistically adjusted for sex, marital status, premorbid functioning, and family history of mental illness. AAO also has been associated with birth complications ([Verdoux et al., 1997](#)), urban residence ([Marcelis et al., 1998](#)), AAO among affected relatives ([DeLisi, 1992](#)), and dopamine receptor genes ([Dubertret et al., 2001](#)). It is thus possible that latitude influences AAO by altering birth complication rates, an urban factor that influences risk, or the frequencies of genes influencing AAO (e.g., dopamine receptor genes). Also, several studies have reported an excess of winter and early spring births among those with

schizophrenia which may be due to a latitudinal factor (Tochigi et al., 2004). If this seasonal pattern is associated with later AAO, then the same factor may also be responsible for the gradient in AAO.

A second possibility is that the factor is among the known correlates of latitude. Many features of the physical environment (e.g., photoperiod, climate) vary with latitude and might influence AAO. Moreover, these physical features produce latitudinal gradients in the biological environment that also could affect AAO. For example, the well-known pattern of greater species diversity towards the equator extends to micro-organisms and other parasites (Nunn et al., 2005), including those that infect and kill humans (Gangestad and Buss, 1993; Guernier et al., 2004). This latitudinal gradient in pathogen diversity allows us to illustrate three general mechanisms by which an environmental factor that varies with latitude could influence AAO.

4.1. Direct effects on individuals

First, the environmental factor could act directly on individuals to increase risk and decrease AAO. For example, prenatal infections are associated with greater risk for schizophrenia, perhaps because infection disrupts neurodevelopment (Brown et al., 2005). Thus, greater pathogen diversity closer to the equator could act directly on individuals to increase risk of schizophrenia and decrease AAO.

4.2. Natural selection on maturation rate

Second, the environmental factor could act indirectly by influencing the evolution of traits (and genes) related to AAO. For example, sexual maturation may be related to AAO because schizophrenia is rare before puberty and most cases begin between ages 15 and 26 (Stevens, 2002). Greater pathogen diversity closer to the equator may contribute to higher human mortality (Teriokhin et al., 2004), which would put evolutionary pressure on humans to mature more quickly and reproduce at an earlier age (Stearns, 2000).

Puberty itself does not predict AAO (Cohen et al., 1999; Ruiz et al., 2000), but AAO might be related to sexual maturation of the brain and consequent mating, which might follow puberty by a shorter interval closer to the equator. For example, the interval between median age at menarche and median age at first live birth in 11 countries ranged from 5 years in Kenya to 11 years in Australia (Morabia and Costanza, 1998). We found a significant correlation between this interval and the latitude of the capital cities of the 11 countries (Pearson

$r=0.72$, $t=3.08$, $df=9$, $p=0.013$), with shorter intervals closer to the equator. The gradient cannot be explained by greater use of oral contraceptives at higher latitudes, because the gradient was also present among women born before the advent of oral contraceptives. Thus, it is possible that greater pathogen diversity closer to the equator leads to earlier onset of schizophrenia by increasing mortality and thereby selecting for an earlier age at reproduction.

Greater pathogen diversity also might decrease the evolved age at reproduction through its effect on sexual selection and mating systems. Among non-human animals, females switch from monogamy to polygyny when males vary so much in quality (e.g., because of pathogen stress) that it is advantageous to mate with the highest quality male, even if that male must be shared with other females (Davies, 1989; Hamilton and Zuk, 1982). The same mechanism might underlie human polygyny, since monogamy is rare in areas of high pathogen stress, and pathogen stress explains 28% of the variation in degree of polygyny worldwide (Low, 1988). Because polygyny is associated with earlier sexual maturation in mammals (Kleiman, 1977), including humans (Kanazawa, 2001), this could lead to earlier reproduction and therefore earlier AAO.

4.3. Sexual selection for condition-sensitive fitness indicators

Sexual selection also produces extravagant traits (e.g., attractive peacock tails) that function as fitness indicators—they vary greatly in some quality (e.g., size, loudness or complexity), and that variation correlates with underlying fitness (Pomiankowski and Moller, 1995; Rowe and Houle, 1996). The opposite sex evolves a preference for the high-fitness, extravagant extreme (e.g., for the peacock with the largest tail) (Kokko et al., 2003). We have proposed that schizophrenia is the low-fitness extreme of a sexually selected fitness indicator that evolved in humans through mutual mate choice (Shaner et al., 2004). According to our hypothesis, human embryos contain genetic instructions to grow brain systems specialized for particular forms of courtship (e.g., verbal courtship). Because these courtship behaviors evolved as fitness indicators, many fitness-reducing mutations and environmental hazards can disrupt development of the necessary brain systems and thereby reduce the attractiveness of courtship behavior. The result is large variation in the trait (e.g., verbal courtship skill) across individuals—variation that correlates with underlying fitness. Our hypothesis is that severe disruption of the necessary brain systems results

in schizophrenia rather than in behaviors recognizable as courtship.

If correct, our hypothesis could explain the latitudinal gradient in AAO, along with many seemingly unrelated facts about the disorder. Its explanatory power arises from the generic properties of all sexually selected fitness indicators, three of which may help explain the latitudinal gradient in AAO. First, animals display fitness indicators most prominently after sexual maturation and during courtship and sexual competition. If schizophrenia is the low-fitness extreme of such an indicator, it should not be apparent to prospective mates until the age at which courtship and sexual competition usually begin. A latitudinal gradient in the age at onset of courtship and sexual competition thus would be expected to produce a similar gradient in AAO. Several proxies for initial sexual behavior, such as age at first sexual intercourse, are proximate determinates of fertility, as well as risk factors for other diseases, such as acquired immune deficiency syndrome. However, we have been unable to find such data, gathered by similar methods across a sufficient range of latitude, to test this prediction.

Second, fitness indicators reflect individual fitness through their sensitivity to general phenotypic condition. We would predict a latitudinal gradient in AAO if there is a latitudinal gradient in general condition (e.g., due to differences in food intake or pathogen prevalence). Greater pathogen diversity towards the equator could increase the rate of infections, reduce overall phenotypic condition, and contribute to the latitudinal gradient in human mortality (Teriokhin et al., 2004). Because the indicator trait (e.g., verbal courtship skill) is expected to be condition-sensitive, this would increase the risk of schizophrenia and decrease AAO. This mechanism is much broader than the one discussed above, in which prenatal infections predispose to schizophrenia. This is because fitness indicators should evolve to be sensitive not only to prenatal infections, but also to a large proportion of all the interactions between genes and environment that determine overall phenotypic condition.

The incidence of schizophrenia is available for only eight of the cities in Fig. 1 (Bresnahan et al., 2003) and does not show a latitudinal gradient across these cities. However, none of the eight cities lie south of 21° north latitude. The incidence of narrowly defined schizophrenia, determined by similar methods, is available for three Caribbean countries (Bresnahan et al., 2003) between 10 and 18° north latitude. When these three countries are included, incidence of schizophrenia does correlate significantly negatively with latitude (Spearman $r = -0.61$, $df = 9$, $p = 0.046$).

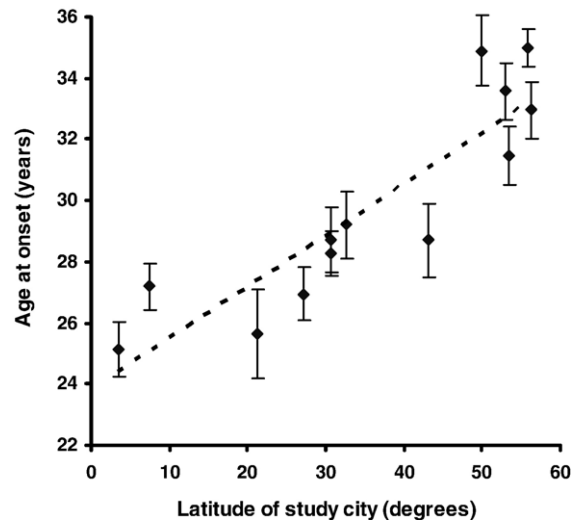


Fig. 1. Latitude and age at onset of schizophrenia in 13 northern hemisphere cities. Data drawn from Jablensky and Cole (1997). In order of increasing latitude the cities were Cali, Colombia; Ibadan, Nigeria; Agra, India; Honolulu, USA; Chandigarh, India (rural and urban); Nagasaki, Japan; Rochester, USA; Prague, Czech Rep.; Nottingham, UK; Dublin, Ireland; Moscow, Russia and Aarhus, Denmark. Bars represent ± 1 SEM.

Third, fitness indicators should evolve greater fitness sensitivity especially under conditions of more intense sexual competition, for example, in populations with high rates of polygyny and/or extra-pair copulations (“infidelity”) (Hasson, 1989; Pomiankowski and Moller, 1995; Rowe and Houle, 1996). This may explain why several studies have reported more favorable outcomes for schizophrenia in developing countries (Craig et al., 1997; Sartorius et al., 1986). Developing countries are closer to the equator, so may have higher rates of infection, mortality and polygyny, as discussed above. If so, they would also have higher frequencies of genes that increase the fitness sensitivity of the indicator trait underlying schizophrenia. As a result, milder impairments in fitness and condition would produce the symptoms of schizophrenia, thereby elevating incidence. However, average outcomes for those with schizophrenia would be better because they would, on average, have milder impairments in fitness and condition.

4.4. A test of competing causal hypotheses

Sensitivity to underlying fitness and general condition also leads to a prediction unique to our hypothesis—the offspring of those who migrate in any direction (except back to ancestral homelands) will develop schizophrenia at a higher rate and with a lower AAO than offspring of those who do not migrate (Table 1).

Table 1
Predicted change in AAO among offspring of migrants^a

Mechanism responsible for latitudinal gradient	Direction of migration		
	Polar	Equatorial	East or west
Direct environmental effect on individuals	↑	↓	None
Natural selection for reproductive maturation rate	None	None	None
Sexual selection for condition-sensitive fitness indicators	↓	↓	↓

^a Change indicated as increased (↑), decreased (↓) or unchanged (none) compared with AAO among offspring of those who did not migrate.

This is because individuals are likely to be best adapted to the environment of their ancestors. Migration to new environments exposes offspring to new hazards (e.g., pathogens, toxins, climates, and social exclusion) to which they are not well adapted. The resulting decrement in fitness and condition could disrupt the development of the indicator trait, increase the risk of schizophrenia, and decrease AAO as well.

In contrast, if the environmental factor acts directly on individuals to influence AAO, then current latitude, not ancestral latitude, will determine AAO. Offspring of migrants to higher latitudes will develop schizophrenia later than offspring of those who remain at lower latitudes, and AAO of migrants will be typical of the higher latitude. Finally, if the environmental factor acts on evolution to vary the frequencies of genes that influence AAO (but does not lead to the evolution of a fitness indicator), then genetic ancestry, not current latitude, will determine AAO. For example, if the environmental factor caused humans at lower latitudes to evolve to reproduce earlier, then offspring of migrants to higher latitudes will share these genes and develop schizophrenia at an age typical of that at lower latitudes.

Thus, in the case of migration towards the poles, the three mechanisms – direct environmental effects, natural selection for reproductive maturation rate, and sexual selection for condition-sensitive fitness indicators – make different and testable predictions about AAO in offspring. Only sexual selection for condition-sensitive indicators predicts earlier AAO. This is important, because several studies have shown a puzzling, several fold increase in the rate of schizophrenia among the offspring of Afro-Caribbean immigrants to European countries (Cantor-Graae and Selten, 2005). These reports do not contain data on AAO, but given the general association between risk and AAO, it is likely that AAO was earlier than expected. If so, then neither

direct environmental effects nor evolved maturation rates can explain it. However, sexual selection for fitness indicators could.

4.5. Life-history traits, fitness indicators and latitude

The age distribution of reproductive effort and the degree of polygyny are among several “life-history traits” that evolve in response to a wide range of environmental factors (e.g., temperature, rainfall, photoperiod, food supply, pathogens, and predators) (Stearns, 2000). Fitness indicators reveal the extent to which individuals are well adapted to the environment in which they developed—the extent to which they have thrived despite environmental hazards. Thus, if schizophrenia is linked to either “life-history traits” or fitness indicators, then its incidence and AAO will correlate with a wide range of environmental factors that can affect health and life span, many of which vary with latitude. We have considered pathogens and mortality, but the same may be true of others including poverty, malnutrition and murder.

5. Conclusions

We have discovered a potential clue to schizophrenia’s cause—its age at onset varies linearly with latitude. People living close to the equator develop the illness about 10 years earlier than those living far from the equator. This is a large effect and understanding it could help explain the causes of schizophrenia. However, there are many potential causes because (1) the key environmental factor could be a feature of the physical environment (e.g., photo period, climate), the biological environment (e.g., pathogen diversity), or the social environment (e.g., degree of polygyny); (2) that factor could act directly on individuals, or indirectly on the evolution of traits (and genes) related to AAO; and (3) the factor could increase disease risk or accelerate the maturation of a trait related to schizophrenia.

To illustrate several general mechanisms, we explored how one potential specific factor, pathogen diversity, might affect AAO. The general mechanisms can be distinguished because they make different predictions about AAO among the offspring of those who migrate towards the poles, so this should be an initial focus of further research. In addition, two mechanisms predict a latitudinal gradient in the age at onset of reproductive behavior, and these could be tested using data on a proxy variable, such as age at first sex, gathered by similar methods across a broad range of latitude.

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