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The urban risk and migration risk factors for schizophrenia: Are cats the answer?

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ABSTRACT

Being born in and/or raised in an urban area is a proven risk factor for developing schizophrenia. Migrating from countries such as Jamaica or Morocco to countries such as England or the Netherlands is also a proven risk factor for developing schizophrenia. The transmission of *Toxoplasma gondii* oocysts to children is reviewed and proposed as a partial explanation for both of these risk factors.

1. Introduction

The epidemiology of schizophrenia is replete with intriguing questions. For example, what causes the 5–8% excess of winter-spring births in individuals who later develop the disease (Torrey et al., 1997b). What accounts for the marked geographic differences in prevalence, such as the unusually low rate among the Canadian Hutterites (Torrey, 1995; Saha et al., 2005)? Why do schizophrenia and rheumatoid arthritis seldom affect the same person (Oken and Schulzer, 1999; Torrey and Yolken, 2001)? Two such questions have become especially prominent in recent years: Why do individuals born and/or raised in urban areas have higher rates, and why do some migrants have higher rates? This paper will briefly review the urban risk factor and migrant risk factor and then propose an explanation for both.

2. Urban risk factor

In 1840 in the United States it was reported that "insanity" had a higher prevalence in the more urban northeastern states than in the rural Midwestern and southern states (Gorwitz, 1966). The 1880 census, the most complete enumeration of mentally ill individuals ever carried out in the United States, confirmed this association between urban residence and higher prevalence of "insanity" (Torrey et al., 1997a). Since 1950, 20 studies of the urban risk factor have been carried out in European countries (March et al., 2008; Kelly et al., 2010). In 18 of the studies individuals born in and/or raised in a large city, compared with a rural area, were significantly more likely to have been diagnosed with psychosis. In most studies the magnitude of the risk factor was approximately two-fold but in one study it was more than four-fold (Eaton et al., 2000). According to one review, the urban risk factor "might explain more than 30% of all schizophrenia incidence." (Van Os, 2004).

Studies have shown that the urban risk factor is related to population density; e.g. in a Danish study the risk for those born in Copenhagen was greater than for those born in the suburbs of Copenhagen, then for those born in other large cities, then small cities, and finally for those born in rural areas (Vassos et al., 2012). The urban risk factor is also dose-dependent; i.e. the more years a child spends in an urban area, the greater the risk (March et al., 2008). Changing one's residence in childhood also changes one's risk. For example, an individual whose family previously lived in a rural area but then moves to Copenhagen more than doubles the relative risk of developing schizophrenia (Marcelis et al., 1999; Pedersen and Mortensen, 2001; Pedersen and Mortensen, 2006a). According to one review, such facts suggest "not only statistical association, but also causality" (Van Os, 2004). Finally, the urban risk factor is relatively specific for schizophrenia; individuals with affective psychoses or depression show much less effect (Eaton et al., 2000; Sundquist et al., 2004).

Many candidates have been proposed as urban risk factors but none have been verified. These include maternal obstetrical complications (Eaton et al., 2000; Harrison et al., 2003); prenatal influenza (Lewis et al., 1992; Westergaard et al., 1999), cannabis use (Lewis et al., 1992) and traffic related exposures (Pedersen and Mortensen, 2006b). Family history of schizophrenia and downward social drift of the parents have also been examined as explanations (Kelly et al., 2010).

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Income inequality, social fragmentation and related social theories have been suggested (Zammit et al., 2010; Kirkbride et al., 2014) but no difference was found in studies of maternal education (Harrison et al., 2003), household crowding (Agerbo et al., 2001), or ethnicity (Sundquist et al., 2004). Given the ongoing rapid urbanization of the world, the identification of the urban risk factor should be a priority.

3. Immigrant risk factor

In the nineteenth century it was widely claimed that "insanity" was more common among immigrants in America. The first systemic study of this problem was Odegaard's 1932 report on an increased incidence of "insanity" among Norwegian immigrants (Odegaard, 1932). For the past three decades there has been much interest in the incidence of psychoses among immigrants to European countries, especially the United Kingdom and the Netherlands. A meta-analysis of 21 such studies reported that immigrants to the UK had a 3–6 times increased incidence of psychoses, and to the Netherlands, a 2–4 times increased incidence; rates for immigrants to other countries were lower (Bourque et al., 2011).

In analyzing the immigrant studies it is important to note that immigrant populations in different countries are very different. The elevated rates in the UK were among Caribbean immigrants, predominantly from Jamaica, Trinidad and Barbados. In the Netherlands the elevated rates were among Caribbean immigrants, predominantly from Surinam and Dutch Antilles, and among Moroccan immigrants. By contrast, the immigrant population in Denmark is predominantly from other Scandinavian and European countries; in one Danish study, 76% of the immigrants came from these countries and only 5% from Africa or the Caribbean (Cantor-Graae and Pedersen, 2007). The living situations for an immigrant from Jamaica or Morocco who moves to London or Amsterdam are obviously different than for an immigrant from Stockholm who moves to Copenhagen.

It should also be noted that the elevation of psychosis rates among immigrants is specific to certain immigrant groups. Turkish immigrants to the Netherlands, for example, do not have increased rates (Selten et al., 2001). Most studies have reported that the increased rates of psychosis are also found in second-generation immigrants (individuals born in the new country to first-generation parents) (Cantor-Graae and Selten, 2005); a recent study suggested that the high rates also carry over to the third generation (Amad et al., 2013). Regarding specificity of psychosis, most of the studies have focused on schizophrenia but a few have also reported increased rates among affective psychoses (Coid et al., 2008).

Many candidates have been proposed to explain the immigrant risk factor but none have been verified. Studies have suggested that misdiagnosis (Harrison et al., 1988), selective migration, or unusually high rates of psychoses in the countries of immigrants' origin are unlikely explanations. Obstetrical complications, cannabis use, substance abuse and infections with the borna disease or influenza viruses have also been investigated with negative results (Fearon and Morgan, 2006; Bourque et al., 2011). Just as is the case for the urban risk factor, researchers have also proposed social explanations, such as discrimination, socioeconomic deprivation, and social defeat ("the chronic stressful experience of outsider status" (Cantor-Graae and Selten, 2005; Veling et al., 2011) to account for the immigrant risk factor.

4. *Toxoplasma gondii* oocysts

We propose that the urban risk and immigration risk factors can be partly explained by exposure to *Toxoplasma gondii* oocysts excreted by cats. The oocysts may infect infants or young children, then later become reactivated in the brain and cause symptoms of psychosis. *T. gondii* is an apicomplexan parasite for which cats are the definitive host. In the absence of perinatal infection, the parasite may be transmitted to humans as an oocyst, from contamination of cat feces, or as a tissue cyst, from eating the undercooked meat from an infected animal. There are suggestions that infection with oocysts is more pathogenic (Dubey, 2004). The rate of seropositivity varies widely by country and by demographic factors such as age and socioeconomic status; in the U.S. it is 10–20% but it is not known how much of that is oocyst or tissue cyst in origin.

The parasite is best known for causing effects on the brain of the fetus when mothers become infected during pregnancy. However, it is also known that *T. gondii* can cause psychotic symptoms; according to one review: "The literature not infrequently focuses attention on psychoses with schizophrenia or schizophreniform features which accompany chronic toxoplasmosis or that acquired in childhood or early in adult life" (Kramer, 1966; Ladee et al., 1966). Having serological evidence of infection with *T. gondii* has also been linked in several studies to suicide attempts (Pedersen et al., 2012; Alvarado-Esquivel et al., 2013) and to cognitive deficits (Yolken et al., 2009). Two studies have reported that individuals with schizophrenia have had more exposure to cats in childhood compared to controls (Torrey and Yolken, 1995; Torrey et al., 2000). And a meta-analysis of 38 studies of *T. gondii* seropositivity in individuals with schizophrenia compared to controls reported an odds ratio of 2.73 (95% CI 2.21–2.38) (Torrey et al., 2012).

Are there plausible mechanisms by which *T. gondii* could cause schizophrenia? *T. gondii* is known to be highly neurotropic, to invade both neurons and glia, and to be widely distributed in the brain. The most likely mechanism by which *T. gondii* could cause schizophrenia is by affecting neurotransmitters. *T. gondii* has the ability to make dopamine (Gaskell et al., 2009) and also to affect host generation of GABA, glutamate, and serotonin with differential effects depending on the strain of the organism (Fuks et al., 2012; Xiao et al., 2013). The immune response to *T. gondii* also results in the generation of cytokines (Fischer et al., 1997) and components of the kynurenic acid pathway (Schwartz and Hunter, 2007), both of which have been thought to play a role in schizophrenia. Finally, *T. gondii* may not cause symptoms directly but rather by facilitating the action of other infectious agents such as endogenous retroviruses (Frank et al., 2006).

Approximately 1% of outside cats excrete oocysts in their feces at any given time, usually when they begin to hunt rodents and birds. They may excrete up to 55 million oocysts per day for a median of 8 days. The oocysts are remarkably hardy, surviving in soil for 18 months; in seawater for 54 months; and even in 2% sulfuric acid for a year (Torrey and Yolken, 2013). In fact, it is not known how long the oocysts do survive since the longevity trials have been terminated before all oocysts have become non-infective. It is also known that a single oocyst can cause clinical toxoplasmosis in pigs (Dubey et al., 1996).

Depending on the number of outdoor cats present, studies have suggested the accumulation of very high numbers of *T. gondii* oocysts in the environment. A study of four California communities, using low and high estimates of the number of oocysts shed per feline infection, estimated that between 9 and 434 oocysts per square foot would accumulate after one year (Dabritz et al, 2007). A similar study of three communities in France estimated the accumulation to be between 3 and 335 oocysts per square foot (Afonso et al., 2010). Another French study took soil samples from 2.3 km^2; 29% were positive and "soil contamination decreased with increasing distance from the core areas of the cat home ranges" (Gotteland et al., 2014). Cats, however, do not defecate randomly but rather prefer areas with loose soil or sand. Thus, a study of cat defecations in a seven acre urban area identified 16 defecation sites, one of which was being used by 15 different cats (Afonso et al., 2008). A study of three public sandboxes in urban Japan video recorded the number of cat defecations; based on these numbers it was calculated that over 18 months the number of accumulated oocysts would have varied from 55,000 to 1.7 million oocysts per square foot of sand (Torrey and Yolken, 2013). Any child playing in such a sandbox would be likely to become infected either through ingestion (e.g. by putting their fingers in their mouth) or inhaling aerosolized oocysts.

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