

NEUROSCIENCE

Maternal Effects on Schizophrenia Risk

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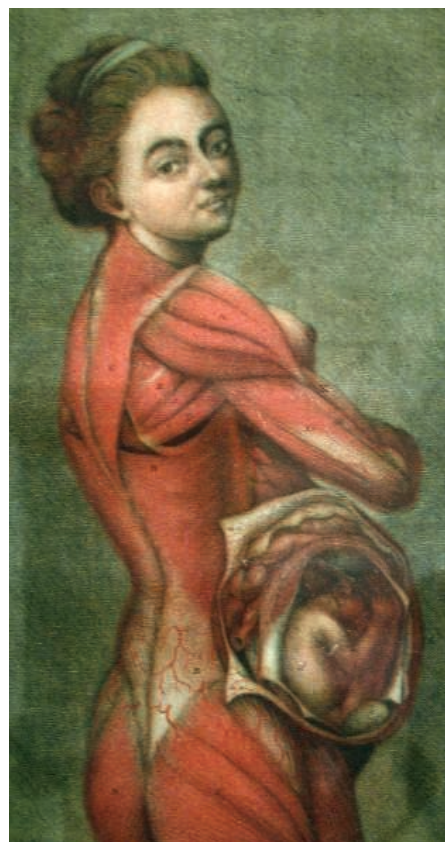
Understandably, there is great enthusiasm surrounding the search for candidate genes that increase the risk for devastating mental disorders such as schizophrenia. Progress is being made on several fronts, such as identifying genes that regulate potential molecular pathways underlying brain development. Genetic variants are also being associated with brain functions during particular cognitive tasks. What is equally important, though, and at risk of being lost in this gene fervor, is a balanced view of the variety of risk factors for mental illness. Many mental disorders are now referred to as “genetic diseases” as if they were autosomal dominant, like Huntington’s disease, in which inheriting a genetic mutation causes the disorder in every person. In the case of schizophrenia, recent epidemiological and animal studies are taking understanding of environmental influences to the molecular level.

Much of the emphasis on the genetics of schizophrenia comes from twin studies, where the incidence of the disorder in genetically identical (monozygotic) twins is 50%. This 50% concordance leaves considerable room for nongenetic influences. However, even that figure may be an overestimate of the role of genetic influence (1). Several lines of evidence point to a key role for maternal environment.

Not widely appreciated in deducing the importance of genes from twin studies is the fact that two-thirds of monozygotic twins share a placenta, which is a key environmental factor. Individual placentas vary with respect to the transport of various nutrients and hormones (2), which affects normal development. Interestingly, X-chromosome inactivation is affected by placental status (3) and, in the largest study of its kind, so is IQ (4). It is therefore possible that the placental environment can influence the expression of genes that are linked to neurodevelopment and schizophrenia. Moreover, indirect evidence suggests that monozygotic twins sharing a placenta have a higher concordance for schizophrenia than monozygotic twins with sepa-

rate placentas (5, 6). It would be extremely informative to directly assess placental status in twin studies of schizophrenia, and there are twin registries where this could be done (7).

Placental status could also influence fetal responses to infectious agents in the mother. For instance, twins sharing a placenta are bathed in the identical blood supply of cytokines that are induced by maternal infection. Moreover, sharing a placenta increases the risk for infection in twins (8). Birth in winter or spring months, when respiratory infections are frequent, is a well-established risk factor for schizophrenia, and most ecological studies of influenza report an increased incidence among offspring born to mothers who were in the second trimester of pregnancy dur-



The maternal environment. Alterations in fetal brain development, and their associated behavioral changes, have been linked to the placental environment in human and animal studies. Image is a color mezzotint from Gautier D’Agoty, *Anatomie des parties de la génération de l’homme et de la femme* (1773).

Local environmental factors impinging on the fetal brain can tip the balance toward mental illness.

ing an epidemic (9). Most importantly, a recent prospective study found that maternal respiratory infection increases the risk for schizophrenia in the offspring three- to sevenfold. Because of the high prevalence of influenza infection, Brown *et al.* estimate that 14 to 21% of schizophrenia cases would have been prevented if maternal infection had not occurred (9). Moreover, there is an association between elevated concentrations of cytokines or antibodies to influenza antigens in maternal serum and the incidence of schizophrenia in offspring (9). Maternal infection may also play a role in the pathogenesis of autism (10), although more epidemiology is needed here. Such links are remarkable, considering that elevated risk may only be in genetically susceptible individuals. If so, the risk associated with maternal infection in that subgroup would be considerably greater than three- to sevenfold.

Although epidemiological studies cannot establish causality, recent work with animals provides experimental evidence that maternal respiratory infection can influence the physiology, behavior, and neuropathology of adult offspring. For instance, maternal influenza infection in rodents causes abnormal behaviors in adult offspring that are consistent with those seen in schizophrenia and autism. These include deficits in social interaction, working memory, prepulse inhibition, and latent inhibition. The latter deficits display postpubertal onset and are normalized by antipsychotic drug treatment. Maternal infection in rodents is also associated with elevated anxiety and neuropathology in offspring that is consistent with that observed in schizophrenia (11, 12).

Changes in the behavior and neuropathology of the rodent offspring are also elicited by injection of synthetic double-stranded RNA into the mother, which evokes an antiviral-like inflammatory response (12–14). Molecular manipulation in this model shows that behavior of the adult offspring results from the balance of pro- versus anti-inflammatory cytokines produced by the mother. That is, blocking pro-inflammatory interleukin-6 or increasing the concentration of anti-inflammatory interleukin-10 strongly attenuates the effects of maternal immune activation on fetal brain development (15, 16). Similar findings have been reported for a model in which

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maternal bacterial infection is mimicked in rodents by injection of lipopolysaccharide, an immunogenic bacterial component (17).

Although a genetic element clearly contributes to schizophrenia and other mental disorders, the maternal-fetal environment must also be taken into account. Environment can alter genetic outcomes and vice versa, and future research must both tease the two influences apart and consider them together to better understand the onset, progression, and treatment of mental disorders.

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ECOLOGY

Thinking Long Term

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Ecologists seeking patterns in populations and environmental correlations dream of coming to grips with lengthy data sets. Usually, animal numbers are determined both by density-independent environmental factors and by density-dependent population processes involving time lags. Disentangling these different factors requires painstaking fieldwork and mathematical skills from the scientists and the patience of Job among funding agencies. Two new analyses of 1000-year-long data series illustrate how long series can reveal insights and improve predictions of pest outbreaks (1, 2).

Caterpillars of the larch budmoth (see the figure, left) can reach densities of 30,000 per tree when they defoliate larch trees and inhibit tree growth, effects detectable as narrow growth rings. Esper *et al.* recently examined larch wood from the European Alps dating back 1173 years (1). The results show that budmoth outbreaks have occurred every 9.3 years on average since 844 C.E.; the authors attribute their absence since 1981 to contemporary warming, which stimulates early egg development and premature hatching. This may be good news for the trees, but is it yet another sign of the effects of anthropogenic climate change?

Thinking of insects' activities more than a thousand years ago recalls biblical accounts of plagues of desert locusts, but there is no continuous historical record of such plagues before the 20th century. However, a Chinese



The value of long-term data. Recent studies of data sets spanning over 1000 years have shed light on the environmental factors that influence the population cycles of larch budmoths (left) and Chinese migratory locusts (right).

Emperor instigated the sporadic collection of data on Chinese migratory locusts (see the figure, right) as early as 707 B.C.E., and his successors maintained a continuous series of annual records from 957 C.E. (3–5). Stige *et al.* have now reanalyzed these data in the context of rainfall and temperature changes (2). As in time series of desert locusts (6), brown locusts (7), and Australian plague locusts (8), the data are not insect numbers but proxies based on numbers of administrative areas infested. Significant relationships with rainfall can be found in all of these locusts, but how rainfall affects the insects' survival may vary according to species, depending on whether they have eggs that can remain dormant for a year or longer and so survive droughts, and on the spatiotemporal distribution of the rain. For the Chinese locusts, Stige *et al.* show that both floods and droughts are important, with temperature and rainfall interacting to set the scene (2). The study also emphasizes the importance of low-frequency phenomena, which involve effects discernible at time scales longer than a year. These are known in many ecosystems and were detected

Thousand-year records of animal population patterns and climate yield insights into the impacts of environmental change.

in desert and brown locusts as unexplained 16- and 17-year cycles, respectively (6, 7).

Previous studies of the Chinese locust (3–5) focused on interannual rather than longer-term variations, with one notable exception showing that population variability increased at longer time-scales (9). Stige *et al.* have now re-examined the data at lower frequencies than annual. In a kind of ecological archaeology, they used mean decadal temperature (derived from ice cores, tree ring data, lake sediments, and contemporary records) and mean decadal rainfall (based on samples of juniper that tally with precipitation indices) to show that there were more locusts when the climate was cold and wet and fewer when it was warm and dry.

The authors find that these climatic effects accounted for locust variability for periodicities of 30 years or more. Decadal frequencies of droughts and floods have a multiplicative effect on the locusts. Both droughts and floods are more common in cold, wet periods, conditions associated with high locust numbers because droughts allow the insects to lay eggs on riverbanks and lakesides; retreating floods also provide ideal breeding conditions. These responses detected at decadal scales have important practical implications: A projected warming Chinese climate would be expected to lead to fewer locusts as a result of a reduced breeding habitat, despite a positive association between locusts and temperature at the annual scale (3).

Frequency-dependent effects of this kind may need to be taken into account to correctly interpret other phenomena liable to disruption by global warming, such as wind systems

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