

nature neuroscience

Of mice and mental illness

A recent conference in Madrid ('Synaptic dysfunction and schizophrenia', sponsored by the Juan March Foundation) demonstrated the immense challenge that schizophrenia presents for neuroscientists. Although the disease has a genetic component, no genes have been identified that reliably predict its occurrence. The concordance rate of only 40–50% for identical twins suggests a significant environmental component, yet none has been identified that is clearly causal. Many changes occur in the brains of schizophrenics, but progress has been disappointingly slow in identifying a diagnostic pathology or biomarker. Furthermore, even within subjects, there is substantial variation in the symptoms that define the disease clinically (delusions, hallucinations, disorganized thoughts, lack of emotion and motivation, social withdrawal, impairments in attention and working memory), which show a puzzling delayed onset in the teens or early twenties.

Despite these challenges, the high prevalence of the disease (1% of the population) and its consequences for victims demand the continued efforts of basic scientists and clinicians. A better understanding of the genetics might provide crucial clues to its root causes, but in the meantime (or in addition), an animal model of some aspects of the disorder could provide valuable insight. The evidence is strong that schizophrenia is a disorder of development, and research on the developing brain may only be possible in animals.

But how would one recognize a delusional mouse? Fortunately for researchers, in addition to the familiar clinical symptoms, schizophrenics also show abnormalities in eye tracking and responding to repeated stimuli—behaviors that can be measured in other animals. (Close relatives of schizophrenics, without clinical symptoms, often show similar deficits.) Some researchers even conclude that these deficits represent the 'core' of the disease because they sometimes present before the onset of full-blown clinical symptoms. However, this claim is controversial because these deficits are shared with other disorders, such as autism, making it less likely that they lead directly to symptoms such as hallucinations.

At the Madrid meeting, Paul Patterson (Caltech) presented some provocative work on an animal model of schizophrenia using maternal viral infection, an idea based on epidemiological data. Whereas other animal models of schizophrenia use specific observations about the disease pathology to reproduce some of its deficits (for example, an early lesion to the hippocampus produces changes in dopamine release that are reminiscent of the disease), the maternal infection model makes no assumptions about which molecules or neural circuits underlie the pathology; if validated, it could be a useful tool for studying the causes of schizophrenia.

Patterson and colleagues based their model on the epidemiological finding that second-trimester maternal respiratory infection increases the risk of schizophrenia in the children. More generally, large population studies have shown that the incidence of schizophrenia is higher in people who were born in urban settings and whose mothers were pregnant in the winter. One interpretation

is that both situations are associated with a higher risk of maternal infection, such as influenza, during pregnancy.

The researchers find that mice born to mothers who are given a respiratory infection at mid-gestation show abnormal behaviors as adults, which resemble disturbances seen in schizophrenics¹. For example, these mice show deficits in 'prepulse inhibition' in an acoustic startle test: after hearing a tone too quiet to cause a startle itself (the prepulse), normal animals show reduced startle to a subsequent louder tone; mice born to infected mothers (and schizophrenic patients) display less prepulse inhibition. Antipsychotic drugs that modify cognitive symptoms in schizophrenics also reduce the deficit in prepulse inhibition in affected mice, suggesting that similar neural circuits are involved. Furthermore, mice born to infected mothers are deficient in exploratory behavior and show decreased social interaction, analogous to some of the so-called 'negative' symptoms that characterize schizophrenia clinically.

The response of the mother's immune system itself may lead to the brain changes: Patterson and colleagues detect no virus in the affected offspring and—more convincingly—can mimic the behavioral deficit by stimulating the maternal immune system in the absence of virus (using a synthetic double-stranded RNA that evokes an anti-viral-like immune response). Observations from another research group that used a different prenatal immune challenge to produce similar behavioral responses support this view². Sick mothers might care for their pups less well than healthy mothers, but preliminary data argue against differences in maternal care as a factor in the behavioral changes seen in offspring.

Patterson reported that in addition to a number of changes in cortex and hippocampus, adult mice born to infected mothers show a loss of Purkinje cells in the cerebellum—specifically in lobules VI and VII of the cerebellar vermis. Related changes occur in schizophrenic patients, although the results are complicated by the potential effects of chronic alcohol abuse in schizophrenics, which is common and can lead to cerebellar pathology.

The human maternal infection explanation is yet to be proved for schizophrenia, and it remains to be seen how closely the mouse model resembles human disease. In particular, many of the behavioral deficits observed in the mouse, and the cerebellar deficit, are shared by other mental illnesses—autism in particular—so the specificity of the model for schizophrenia is controversial. It will be interesting to determine whether the behavioral deficits depend on the time of infection during pregnancy (as the human epidemiology indicates), and whether mice born to infected mothers show late onset of symptoms as seen in schizophrenia. In any case, it should now be possible to determine how the mother's immune response can lead to changes in the brain and altered behavior, which could generate testable hypotheses about the causes of schizophrenia.

1. Shi, L., Fatemi, S.H., Sidwell, R.W. & Patterson, P.H. *J. Neurosci.* 23, 297–302 (2003).
2. Borrell, J., Vela, J.M., Arevalo-Martin, A., Molina-Holgado, E. & Guaza C. *Neuropsychopharmacology* 26, 204–215 (2002).