

# The Promise of Epidemiologic Studies: Neuroimmune Mechanisms in the Etiologies of Brain Disorders

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We present our views on current and past epidemiological contributions to our understanding of neuroimmune mechanisms for neurodevelopmental disorders, such as schizophrenia. We also discuss future directions for epidemiological studies and ways in which newer cohorts are well positioned to address questions that were previously not feasible to explore.

Epidemiologic studies have made powerful contributions to the understanding and prevention of neurodevelopmental disorders. Some of these contributions are famous, for example, the work on neural tube defects, which ultimately demonstrated that maternal periconceptual folate supplements reduce the risk among their offspring (Susser et al., 2008). Others are less widely known, such as the recent advances that have been made for schizophrenia, where epidemiologic findings are being replicated and suggesting pathways for neuroscience research. These findings include—but are not limited to—the high risk of schizophrenia among minority groups in Western Europe, among offspring of older fathers, and among offspring of mothers exposed to famine in early gestation (March and Susser, 2006).

Moreover, the scope of epidemiologic research on neurodevelopmental disorders is growing exponentially. Many large cohorts have now been followed prospectively from in utero up to young adulthood (Susser et al., 2000). Another set of very large cohorts (100,000 or more) have recently been established or are in the process of being established, with in-depth measures of prenatal experience, archived biological specimens, and follow-up of neurodevelopmental outcomes. National registries have been established in many countries—most notably Scandinavian countries—which allow us to study millions of people, via linkage of population registries, birth registries (and sometimes archived prenatal biological specimens),

and treatment registries. Finally, the importance of collaboration across large cohorts and across national registries is increasingly recognized and much facilitated by developments in informatics. These and other developments have brought us into a new era for epidemiologic studies of neurodevelopment.

But much of the groundwork has already been laid. To illustrate the evolving contribution of epidemiological research toward advancing our understanding of neuroimmune interactions, we use the example of prenatal infection and schizophrenia, for which the potential importance of neuroimmune processes has become quite evident.

## Epidemiological Evidence Linking Prenatal Infection and Schizophrenia

The first epidemiological studies linking prenatal infection to schizophrenia were ecologic studies. Although there are some conflicting findings, many of these studies found that mothers who were pregnant during an influenza epidemic had offspring with an increased risk of schizophrenia (Brown, 2006). Nevertheless, ecological studies are limited by the inability to determine whether infection actually occurred, given that infection is assumed based on events that occur for an entire population. In fact, it is possible that offspring of mothers who did *not* manifest influenza symptoms may have been at greatest risk, as these mothers may have had the most vigorous immune response to influenza exposure.

Subsequently stronger epidemiological evidence linking prenatal infection to schizophrenia was derived from longitudinal cohort studies that prospectively collected obstetric information (including maternal sera during pregnancy in some studies) and identified those who developed schizophrenia or other psychotic disorders. Generally these studies compared the individuals who developed schizophrenia with a sample of those who did not, a strategy known as a “nested case-control” design (Susser et al., 2006). Although there has not been complete consistency among these studies, a series of infections during pregnancy (ascertained from medical chart reviews and/or serological analyses of archived maternal sera) have been associated with risk of schizophrenia in offspring, including influenza, rubella, maternal upper respiratory infections, genital reproductive infections, and herpes simplex virus-type 2 (HSV-2) (Brown, 2006). Immunologic evidence of prior exposure to *Toxoplasma gondii* has also been associated with schizophrenia (Brown, 2006).

A puzzle presented by these data is the wide range of infections for which associations have been reported. Since none of these findings are yet definitive, one explanation is that many are false positives, and we have yet to determine the one or few that are truly related to schizophrenia. Until now, almost all studies with biological measures of prenatal infection have shared certain limitations, such as small sample sizes.

Another possibility is that various infectious exposures exert effects by a common mechanism, for example, by invoking an immune response. Indeed, evidence from animal studies suggests that most viral infections do not appear to cross the placenta; therefore, the teratogenic influences might be more related to maternal, fetal, and/or placental responses to infection (Patterson, 2009). Given this possibility, two nested case-control studies examined the relationship between fetal exposure to elevations in a panel of maternal proinflammatory cytokines during pregnancy and risk for schizophrenia in offspring (Brown et al., 2004b; Buka et al., 2001). The first study found an association between maternal tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) levels at birth with increased risk of schizophrenia in offspring, whereas the second study found an association between fetal exposure to the maternal chemokine, interleukin-8 (IL-8) during the second/third trimesters and risk for schizophrenia in offspring (Brown et al., 2004b; Buka et al., 2001). Although both of these cytokines are associated with inflammation, it remains unclear whether exposure to specific cytokines during specific periods of gestation portends greater risk for subsequent psychopathology in offspring. Again, these studies were faced with limitations in sample size and measurement which can be overcome in the current era.

In a similar vein, there have been inconsistent findings concerning which period(s) during pregnancy incur the most risk for subsequent difficulties in offspring. Many of the ecologic studies examining exposure to an influenza epidemic during pregnancy have found that the second trimester may be particularly important in portending increased risk for schizophrenia (Brown, 2006). However, the first study using serologically documented influenza infection from archived maternal sera found that exposure in early gestation was most important and found no impact of third-trimester influenza exposure (Brown et al., 2004a). Further, a second study with prenatal sera, which had samples only from birth (corresponding to infection in the third trimester), found that third-trimester influenza exposure was related to increased risk of schizophrenia among

offspring (Ellman et al., 2009). Studies of other factors have found evidence for effects in both early (e.g., maternal starvation, maternal bereavement, maternal rubella) and late (e.g., hypoxic events) gestation (Cannon et al., 2002).

Some of these apparently discrepant findings on timing of exposure may not hold up over time. Nonetheless, it is possible that there are sensitive periods where the fetus is especially vulnerable to exposure to infection and immune responses associated with infection and that these sensitive periods differ depending on the infectious agent—or even the particular strain of an infectious agent (Ellman et al., 2009)—and the subsequent neurodevelopmental sequelae.

It is also possible that fetal exposure to infection only incurs risk in individuals who have a preexisting vulnerability associated with schizophrenia. Specifically, one study found that fetal exposure to influenza B led to decreases in cognitive performance among 7-year-olds who later developed schizophrenia in adulthood, but not among control children who had no evidence of psychiatric morbidity in adulthood (Ellman et al., 2009). Another study found that the influence of fetal exposure to maternal pyelonephritis (urinary and bladder infections) on risk for schizophrenia was only evident in those who had a family history of a psychotic disorder (Clarke et al., 2009). Although these findings are suggestive of gene-environment interactions, no study has directly tested whether specific genetic polymorphisms make certain individuals more vulnerable to the effects of infection and immune-related conditions.

### Neuroimmune Mechanisms in the Current Era

Neuroimmune mechanisms are now being considered as potential risk factors for a wide range of neuropsychiatric outcomes (e.g., Patterson, 2009). With the vastly greater scope and precision of epidemiologic investigations, and the advancing technology for measuring genetic and biological factors, the opportunities for epidemiologic studies of these processes are enormous.

First, we can now examine the effects of specific exposures—such as prenatal starvation, increased paternal age, and specific strains of infection—on neuroim-

mune processes and potential mechanisms for these effects such as mutagenesis and epigenetic modifications. Second, the role of timing of the prenatal exposure can be investigated with much more precision. Third, we can examine the possibility that some individuals are genetically susceptible to these exposures (Ellman et al., 2009), for example, carry genetic polymorphisms that are associated with increased inflammatory responses or dysregulation in immune functioning. Fourth, we can study genetic and other maternal characteristics which potentially contribute to immune functioning of mothers during pregnancy and subsequent risk for psychopathology in offspring. Body mass index, exercise, sleep, and health-risk behaviors (e.g., substance use and abuse) have all been linked to alterations in immune functioning and susceptibility to infection and disease (e.g., Irwin et al., 2008; Segerstrom and Miller, 2004). Fifth, we can begin to study fetal sex by immune interactions in the pathogenesis of neurodevelopmental disorders, which has been relatively understudied (Ellman et al., 2008). Finally, the newer epidemiological studies have the potential to map out the relationship between early immune-related exposures and important intermediate phenotypes throughout development, such as cognitive functioning, brain development, and social functioning, which ultimately could lead to targets for early intervention. It is only in the current era that we have the power and technology to arrive at definitive answers to these questions.

### Conclusion

Intriguing epidemiologic evidence on prenatal infection and schizophrenia exemplify the plausibility of neuroimmune mechanisms for mental disorders but also the limitations of available evidence. In the current era, we are already shifting to larger epidemiologic studies with more precise measures of multiple prenatal exposures and indicators of neuroimmune status. These studies can examine more definitively whether prenatal infections (or other exposures) are related to schizophrenia. Lastly, although we have often used schizophrenia as an example, it is imperative for epidemiological investigations to determine whether

immune-related risk factors portend increased risk for disorders other than schizophrenia or phenotypes that are shared between disorders. Current epidemiological investigations are well positioned to tackle many of these questions, which could lead to results that will greatly inform primary prevention and early intervention strategies for mental disorders.

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