The Kraepelinian Dichotomy From the Perspective of Prenatal Infectious and Immunologic Insults

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The “Kraepelinian dichotomy” between schizophrenia (SZ) and bipolar disorder (BD) has been a dominant force in our thinking on the classification of these mental disorders. Emerging evidence indicates that these 2 disorders overlap significantly with regard to epidemiology, clinical presentation, genetic susceptibility, structural neuroanatomy, and treatment. Prenatal infection and immunologic dysfunction appear to be risk factors for both SZ and BD; some of these gestational exposures are present in both disorders while others may be specific to 1 or the other of the 2 syndromes. In this paper, we shall review prior studies of prenatal infections and immunologic insults in schizophrenia and BD, including exposures which overlap and which differ between these disorders, discuss the potential utility of maternal infection as one strategy toward developing a more biologically meaningful diagnostic classification system, and propose new recommendations for future research aimed at dissecting these 2 disorders from one another at the etiologic level.

Key words: schizophrenia/bipolar disorder/infection/immunology/epidemiology/Kraepelin/prenatal/birth cohort/risk factor

The “Kraepelinian dichotomy” between schizophrenia (SZ) and bipolar disorder (BD) has been a dominant force in our clinical and research discourse for decades. Recent evidence, however, suggests that these 2 disorders overlap significantly with regard to their epidemiologic features, clinical presentation, familial aggregation and susceptibility genes, structural neurobiology, and treatment response.1–9 Indeed, Kraepelin himself noted “It is becoming increasingly clear that we cannot distinguish satisfactorily between these 2 illnesses (dementia praecox [SZ] and manic depressive psychosis [BD]).”10 In the present article, we aim to: (1) review previous studies of prenatal infections and immunologic insults in SZ and BD; (2) discuss the potential utility of these environmental exposures with regard to development of a new nosology of these disorders; and (3) discuss strategies for future research aimed at dissecting these 2 disorders from one another at the etiologic level.

A Brief Overview of Early Developmental Risk Factors for BD

Although a considerably larger body of evidence has implicated a neurodevelopmental etiology for SZ11 than for BD, an appreciable amount of data suggest that prenatal and postnatal brain developmental insults may also be of relevance to BD. Though not identified in all studies, certain premorbid disturbances, including delayed motor milestones, lower cognitive test scores, impaired adolescent adjustment, and school performance have been observed in individuals who later develop BD.12–15 Maternal exposure to the Dutch Hunger Winter of 1944–1945 during the second and third trimesters has been related to risk of BD.16,17 Moreover, preterm birth, low birthweight, fetal/neonatal hypoxia, other obstetric complications, and advanced paternal age have been observed to occur at increased rates in some studies of BD.18–25 Recently, oxytocin administration to induce delivery was found to be related to an increased risk of BD later in life.26 Of particular relevance to maternal infection and inflammation, patients with BD tend to be born more commonly during the winter and early spring.27 Consequently, our group and others have investigated whether prenatal exposure to infectious pathogens and immunologic abnormalities (eg, altered cytokine levels) during pregnancy confer an elevated risk of BD among offspring.
Maternal Influenza and *Toxoplasma gondii* in SZ and BD

Maternal exposure to influenza has been associated with SZ (for review, see Brown and Derkits). The vast majority of these studies were based on ecologic data, i.e., maternal influenza as defined from epidemics in populations; these studies, however, are prone to diagnostic misclassification. In the birth cohort of the Child Health and Development Study (CHDS), in northern California, our group assayed archived maternal serum specimens for influenza antibody among cases who later developed SZ and matched comparison subjects. In that study, we demonstrated that maternal influenza documented by antibody to this pathogen in the first half of pregnancy was related to a 3-fold increased risk of SZ following exposure. Following on this finding, we aimed to evaluate whether maternal influenza during pregnancy was a risk factor for BD in this same birth cohort. In the first of our studies, which was based on prospective physician diagnoses of maternal influenza, we found that influenza was related to a greater than 4-fold, statistically significant increased risk of BD. The findings were similar following restriction to BD I disorder. Interestingly, the strongest association between maternal influenza and BD was found for BD with psychotic features, with an odds ratio approaching a 6-fold increase.

In order to confirm the finding, we assayed archived prenatal maternal serum specimens in BD cases and controls from this birth cohort for antibody to the influenza strains circulating in the population during the period of the pregnancies. A similar method was used as in our study of SZ in the CHDS birth cohort. Serologically documented maternal influenza was associated with a greater than 5-fold increased risk of BD, similar to the effect size observed for clinically diagnosed maternal influenza and BD. In contrast, there was no increase in risk of BD without psychotic features following maternal influenza exposure by serologic assessment. One limitation of the study was the fact that the conventional 4-fold rise in antibody titer was not used to diagnose influenza due to a lack of sufficient subjects with serial samples, though the antibody titer cutoff used to define influenza exposure had been validated previously in relation to a 4-fold rise in influenza antibody titer.

Some prior studies supported a possible association between prenatal influenza and BD. In the British Perinatal Mortality survey, influenza and pyrexia were associated with affective psychosis, though the study utilized diagnoses from case notes and there was no separate analysis of unipolar and bipolar psychosis. In another study, which relied on maternal recall of influenza, an association with BD at a statistical trend level was reported. In an additional epidemiologic study, mothers who attended antenatal clinics and who reported influenza during pregnancy had no increase in risk of BD among offspring, though the study was limited by the potential for exposure misclassification and a small sample size.

An ecologic study of influenza epidemics demonstrated a correlation with affective disorders, though the study did not find an association with BD specifically, nor did a second ecologic study of influenza epidemics. Ecologic studies are also limited to a larger extent than other studies by exposure misclassification and confounding.

In the CHDS birth cohort, we demonstrated a greater than 2-fold increased risk of SZ for high *T gondii* antibody titers. This finding has been independently replicated in national birth cohort studies in Denmark and Sweden, each of which used neonatal *T gondii* IgG antibody in filter paper blood spots (neonatal *T gondii* antibody derives from the mother since the fetus cannot generate antibodies at this stage of life). Three previous studies have been conducted on maternal antibody to *T gondii* and affective psychosis/BD. In the Collaborative Perinatal Project, maternal exposure to *T gondii* antibody of the type I strain was related to an increased risk of psychoses in offspring. The finding was particularly strong for cases with affective psychoses, though BD was not examined specifically. No association was observed between maternal seropositivity for *T gondii* and affective or BD in a Danish sample, but the sample size was small. In a study utilizing neonatal filter paper blood spots in a larger sample from Denmark, no associations were observed between *T gondii* and BD in offspring.

That study was limited by a relatively young sample. Hence, it appears that maternal influenza may be a risk factor that crosses diagnostic boundaries between SZ and BD with psychotic features, but curiously, the association does not seem to exist for nonpsychotic BD. This suggests that maternal influenza may increase risk of psychosis, rather than SZ per se, among offspring. With regard to maternal *T gondii*, 3 studies have demonstrated associations for SZ, while 2 studies of prenatal *T gondii* and BD were negative. The only positive study of *T gondii* and BD showed an association only for the type I strain; since previous studies did not subtype this antibody by strain, they are not comparable with one another. Thus, the weight of evidence suggests that maternal *T gondii* is a risk factor for SZ, but possibly not BD. The findings for maternal influenza and maternal/neonatal *T gondii* with regard to SZ and BD are summarized in table 1.

Other Maternal Infections and Immunologic Abnormalities

In a previous article, we provided a detailed review of the literature on maternal infections as risk factors for SZ (for review, see ). In addition to the maternal influenza and *T gondii* associations reviewed above, maternal IgG antibody to herpes simplex virus type 2 (HSV-2) were found to be associated with SZ, though another study was negative. One previous study of BD, from Denmark, examined relationships to prenatal HSV-2. In that study, which used neonatal dried blood spots, seropositivity to HSV-2 was not related to BD. Other infectious agents...
Table 1. Serologic Studies of Maternal Infection in Schizophrenia and Bipolar Disorder

<table>
<thead>
<tr>
<th>Maternal Infection</th>
<th>Cohort/Country</th>
<th>Source of Sera</th>
<th>Schizophrenia</th>
<th>Bipolar Disorder</th>
</tr>
</thead>
<tbody>
<tr>
<td>Influenza</td>
<td>CHDS</td>
<td>Maternal</td>
<td>3-fold increased risk&lt;sup&gt;31&lt;/sup&gt;</td>
<td>4.5-fold increased risk&lt;sup&gt;26&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>CHDS</td>
<td>Maternal</td>
<td>3-fold increased risk&lt;sup&gt;36&lt;/sup&gt;</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>Denmark</td>
<td>Neonatal</td>
<td>Nearly 2-fold increased risk&lt;sup&gt;32&lt;/sup&gt;</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>Sweden</td>
<td>Neonatal</td>
<td>3-fold increased risk&lt;sup&gt;38&lt;/sup&gt;</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>CPP</td>
<td>Maternal</td>
<td>—</td>
<td>5-fold increased risk (type I strain only)&lt;sup&gt;39&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Denmark</td>
<td>Maternal</td>
<td>—</td>
<td>No association&lt;sup&gt;37&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Denmark</td>
<td>Neonatal</td>
<td>—</td>
<td>No association&lt;sup&gt;40&lt;/sup&gt;</td>
</tr>
<tr>
<td>Toxoplasma gondii</td>
<td>CHDS</td>
<td>Maternal</td>
<td>No association&lt;sup&gt;44&lt;/sup&gt;</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>CPP</td>
<td>Maternal</td>
<td>1.6-fold increased risk&lt;sup&gt;42&lt;/sup&gt;</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>Denmark</td>
<td>Neonatal</td>
<td>1.6-fold increased risk&lt;sup&gt;45&lt;/sup&gt;</td>
<td>No association (including HSV-2, HSV-1, CMV)&lt;sup&gt;40&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

Note: CHDS, Child Health and Development Studies (United States); CMV, Cytomegalovirus; CPP, Collaborative Perinatal Project (United States); HSV-1, herpes simplex virus type 1; HSV-2, herpes simplex virus type 2.

examined in that study, including herpes simplex virus type 1 (HSV-1) and cytomegalovirus, were also not related to BD. On the other hand, in the CHDS birth cohort, clinically diagnosed maternal genital/reproductive infections were related to a greater than 5-fold increased risk of SZ, but this study was not able to specify particular G/R infections.<sup>45</sup>

With regard to pro-inflammatory cytokines, increased maternal interleukin-8 and tumor necrosis factor-α, both collected during pregnancy, were associated with SZ in offspring.<sup>46,47</sup> Two studies have been conducted on neonatal inflammatory biomarkers and SZ. The first, from Denmark, showed that 17 such biomarkers did not differ between SZ cases and controls.<sup>48</sup> The second, from Sweden, examined neonatal acute phase proteins, which are produced in response to inflammatory cytokines.<sup>49</sup> Levels of serum amyloid A and procalcitonin were decreased in neonatal blood of patients who later developed SZ; the authors argue that these subjects may have been more susceptible to infection. It should be kept in mind that studies of maternal, in contrast to neonatal cytokines, are measuring different constructs. Notably, maternal cytokines become markedly increased at the time of parturition and this might affect neonatal cytokine levels. In contrast, maternal cytokine levels are more likely to reflect pregnancy-related inflammatory factors, including infections, apart from factors during late pregnancy and the peripartum period; consequently, it is not surprising that the findings from studies of maternal and neonatal cytokines differ. To date, there are no published studies on prenatal or neonatal cytokines in relation to BD in offspring.

In summary, the literature on serologically documented prenatal/neonatal HSV-2 and SZ is mixed while there is some evidence that it is not related to BD. Further work is needed to clarify these distinctions and to examine other prenatal infections and immune disturbances in these disorders. The serologic findings for maternal/neonatal herpesviruses are summarized in Table 1.
illnesses. In a study of offspring born to pregnant women supplemented with phosphatidylcholine, Ross et al\(^5\) demonstrated that this intervention led to greater suppression of the P50 auditory evoked potential; deficits in this measure of cerebral inhibition have been observed in SZ, suggesting a potential preventive strategy. Translational studies may shed further light on the link between maternal infection and pathogenic mechanisms. Animal models have demonstrated that maternal immune activation causes behavioral and brain anomalies in offspring that are analogous to those found in severe mental illnesses; while many of the outcomes are observed in SZ, they also been found in BD, other psychoses, autism, and other psychiatric diagnoses (for review see Meyer et al\(^52\)). Second, a better understanding of how etiologic risk factors cross diagnostic boundaries should serve to provide more precise estimates of how preventive interventions affect public health. For example, if influenza is a risk factor for psychosis in general, rather than SZ per se, one may expect a significantly greater population attributable risk of such outcomes stemming from this exposure. Third, the focus on the exposure, rather than on the clinical diagnosis, may lend itself to a better understanding of the biological phenotype. In a previous study, we demonstrated that increased levels of the cytokine IL-8 were associated with cerebral ventriculomegaly\(^53\) and prenatal infections were related to deficits in executive functions.\(^54\) This provides proof of principle that meaningful biologically defined subgroups of cases could be linked to biomarker-defined risk factors. Hence, implementation of systematic efforts including banking of biospecimens during the prenatal period should be given high priority.

**Conclusions and Future Directions**

While Kraepelin is appropriately credited with the seminal efforts toward deconstructing SZ and BD at the clinical level, he was tentative regarding the boundary between these disorders, in large part because of the lack of objective data available at that time.\(^10\) In this vein, we have presented evidence from one class of prenatal risk factors that should serve as a model for an approach to establish new boundaries between subtypes of psychiatric disorders that are more reflective of biological processes rather than sets of symptoms and behaviors. This holds promise toward identifying new pathogenic mechanisms for prevention, early intervention, and treatment. The findings on maternal influenza indicate that the separate examination of BD with vs without psychotic features will be an important approach in future efforts toward deconstructing the effects of prenatal infection on risk of SZ and BD.

Toward this end, we propose 4 key goals for future research involving the use of maternal infectious and immune related disturbances to examine the boundaries between SZ, BD, and other psychiatric conditions. First, it will be necessary to systematically examine prenatal biomarkers indicative of these exposures and different outcomes using the same methods for defining the exposures, outcomes, and potential covariates. This can best be done if all of these measures are obtained within the same birth cohort so that differences in protocols for measurement and other factors that can produce bias are minimized across exposures and outcomes. Initial attempts to conduct this type of research in birth cohort studies are exemplified by some of the studies reviewed above. A broad array of diagnoses, including not only psychotic disorders, but also autism, major depressive disorder, and anxiety disorders should be included in such investigations. Second, these early prenatal infectious exposures should be examined in relation to biologically meaningful phenotypes such as those revealed from neuroimaging protocols, neuropsychological assessments, and electrophysiologic studies across diagnoses. Third, because the type of outcome of a given environmental exposure is likely dependent on familial vulnerability including those due to common and rare genetic variants, a comprehensive battery of both environmental and genetic measures should be obtained in not only probands and their mothers, but also other family members. Fourth, given the significant functional consequences of severe mental illnesses, including unemployment, physical comorbidity, and hospitalization, which also cross diagnostic boundaries, these outcomes should also be examined in relation to maternal infection and immunologic insults.

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