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Maternal immune activation and preeclampsia

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Thesis

MATERNAL IMMUNE ACTIVATION AND PREECLAMPSIA

by

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Tami Segal
ACKNOWLEDGMENTS

Thank you to the professors and mentors who guided me through this project.
Schizophrenia and autism are debilitating illnesses thought to have developmental etiologies. Prenatal brain damage can alter brain development and cognition leading to the pathologies of both diseases. Furthermore, prenatal infections have been implicated as a risk factor for both schizophrenia and autism in large, population-based studies. Many studies have investigated the effects of prenatal infections on brain development and have established inflammatory cytokines as the most likely mediators of brain damage. While preeclampsia exposes a fetus to a similar inflammatory environment as a prenatal infection, a comprehensive review of the work connecting obstetric complications to autism and schizophrenia has not been conducted. The mechanisms explaining the induction of altered brain function after fetal neuroinflammation also requires further study in the specific context of preeclampsia, especially in regards to what factors may differentiate autism from schizophrenia in the course of disease development.
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LIST OF ABBREVIATIONS

ASD................................................................. Autism Spectrum Disorder
BBB................................................................. Blood brain barrier
BDNF............................................................. Brain derived neurotrophic factor
BU ..................................................................... Boston University
CHARGE ......................................................... Childhood Autism Risk from Genetics and Environment
CDC ................................................................. Center for Disease Control and Prevention
CI ..................................................................... Confidence Interval
CNS ................................................................... Central nervous system
DSM-IV ............................................................ Diagnostic and Statistical Manual-IV
DZ ..................................................................... Dizygotic
ICD-8, ............................. International Classification of Disease and Related Health Problems-8
ICD-9, ............................. International Classification of Disease and Related Health Problems-9
ICD-10, ........................... International Classification of Disease and Related Health Problems-10
IL-6 ................................................................. Interleukin-6
IL-8 ................................................................. Interleukin-8
IL-10 ............................................................... Interleukin-10
IL-1β ............................................................... Interleukin-1β
MIA .................................................................. Maternal Immune Activation
MZ .................................................................... Monozygotic
OR ................................................................... Odds Ratio
PE...................................................................................................................... Preeclampsia
PDD-NOS .................................................. Pervasive development disorder- Not otherwise specified
RDS .................................................................................................................... Research diagnostic criteria
SSD .................................................................................................................. Somatic Symptom Disorder
TNF- α............................................................................................................. Tumor necrosis factor α
INTRODUCTION

Exposure to an inflammatory response in utero has been implicated as a possible risk factor for schizophrenia and autism (ASD) (Meyer, Feldon, & Dammann, 2011). Acute neuroinflammation during fetal development may be responsible for some of the shared characteristics of these two disorders (Bilbo & Schwarz, 2009). Schizophrenia and ASD are characterized by deficits in cognition, sensorimotor gating, emotional processing, and executive function to varying degrees as well as structural abnormalities in the insular cortex, cerebellum, and fusiform gyrus (Cheung et al., 2010; Rapin & Tuchman, 2008). Additionally, both groups display reduced brain activity in the prefrontal cortex, amygdala, and fusiform gyrus during social cognition tasks (Pinkham, Hopfinger, Pelphrey, Piven, & Penn, 2008). Further examples of the shared and specific pathologies of these diseases are outlined in Table 1. The nature and extent of symptoms may vary due to the timing and severity of exposure to inflammation.

Preeclampsia is associated with an inflammatory response similar to that launched by an infection. While many studies have implicated maternal infections in the etiology of both disorders, a comprehensive and dedicated review of the impact of preeclampsia has not been conducted, nor is there an established mechanism by which inflammation could give rise to the pathologies associated with these disorders.
Table 1. Autism and Schizophrenia: Related but Opposite Diseases

<table>
<thead>
<tr>
<th>Autism</th>
<th>Both</th>
<th>Schizophrenia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Repetitive behavior</td>
<td>Social withdrawal</td>
<td>Paranoia</td>
</tr>
<tr>
<td>Symptoms begin early in life</td>
<td>Communication impairment</td>
<td>Symptoms generally begin in early adulthood</td>
</tr>
<tr>
<td>Increased gray and white matter</td>
<td>Poor eye contact~negative symptoms of schizophrenia</td>
<td>Reduced grey and white matter</td>
</tr>
<tr>
<td>Smaller corpus callosum</td>
<td>Larger corpus callosum</td>
<td></td>
</tr>
<tr>
<td>Larger, more dense amygdala</td>
<td>Smaller amygdala, less reactive</td>
<td></td>
</tr>
<tr>
<td>High BDNF</td>
<td>Low BDNF</td>
<td></td>
</tr>
</tbody>
</table>

While autism and schizophrenia are characterized by shared abnormalities, the diseases are often opposite in pathology. Both diseases are associated with abnormal corpus callosum density, however schizophrenics tend to have hyperdevelopment in this area while autistics are hypertrophied. The fact that there is an overlap in the pathways altered in both diseases suggests they may have common etiology and genetic or environmental factors result in different outcomes for how these pathways are altered (Crespi & Badcock, 2008).

Schizophrenia is a devastating psychological disorder that affects between 0.5 to 1% of the world population (“CDC - Burden of Mental Illness - Mental Illness - Mental Health Basics - Mental Health,” n.d.). In most cases, the disease is diagnosed before the age of thirty, typically 21 years of age for men and 27 years for women. In addition to the emotional cost, Schizophrenia was estimated to cost 2.02 billion Canadian dollars in 2004 due to medical and non-medical cost, and an additional 4.83 billion Canadian dollars due to morbidity, unemployment, and loss of productivity. An American study conducted in 2002 estimated the cost of schizophrenia to be $62 billion in the United States with half of that cost being indirect costs not related to healthcare (Wu et al., 2005). Despite
drastic differences in healthcare systems between these two countries, the cost of schizophrenia is roughly equal in both countries when adjusting for population. The highest economic impact of schizophrenia is associated with onset of the disease, or within one year of the first episode of illness ("CDC - Burden of Mental Illness - Mental Illness - Mental Health Basics - Mental Health," n.d.). Therefore, a better understanding of risk factors for schizophrenia and monitoring those who are at high risk until past the age of 30 may reduce the financial and social cost as well as the outcome of the disease.

Autism is characterized by severely impaired communication and social interaction in addition to repetitive behaviors (Rapin & Tuchman, 2008). ASD occurs in 1% of the population, however the prevalence may be increasing to either environmental factors or increased awareness of the disease leading to changes in diagnostic practices (Fombonne, 2009). Prior to the DSM-V, PDD-NOS, Asperger’s, autistic disorder, and childhood disintegrative disorder were separately defined. These disorders are now collectively referred to as “autism spectrum disorders” (ASD) in the DSM-V. Diagnosis of ASD is generally made early in life when developmental milestones are not met. Deficits in communication are apparent as early as six months.

*Environment, Immunity and Mental Illness*

A prominent hypothesis for the etiology of Schizophrenia suggests that a congenital predisposition primes certain individuals for susceptibility to the disease after environmental stressors in adolescence (Feigenson, Kusnecov, & Silverstein, 2014). This “two hit hypothesis” accounts for the late onset of initial symptoms and the variability in
outcomes for those with genetic markers of schizophrenia. In reviews of a large body of studies, Feigenson et al (2013) and Khandaker et al (2013) provide evidence that a “first hit” can be provided not only by genetic traits, but also harmful prenatal environmental exposures such as maternal infection during pregnancy (Feigenson et al., 2014; Golam M. Khandaker, Zammit, Lewis, & Jones, 2014).

The same immunological insult that can prime a brain for schizophrenia can also cause changes in development that manifest as autism, instead. Several studies have investigated behavioral deficits reminiscent of autism in mice exposed to inflammation in utero (Hsiao & Patterson, 2011). Such mice exhibit increased grooming behavior, deficits in social interaction, and exploratory behavior as symptoms of behavioral abnormalities that correlate with autism in humans. Furthermore, the differences in timing and severity of prenatal neuroinflammation may be responsible for the different pathologies seen in schizophrenia and autism despite their possibly shared etiology.

**Preeclampsia Immunology**

There is currently lack evidence showing the causal relationship between the exposure to preeclampsia during fetal development and incidence of schizophrenia and ASD. Preeclampsia is a multifactor disease in which a developing fetus can be exposed to a number of environmental stressors, including inflammatory cytokines. Preeclampsia is a hypertensive disorder that occurs in 5-8% of pregnancies. It is defined by either a systolic blood pressure of >140 or a diastolic pressure of >90 mmHg in addition to proteinuria. The cause of preeclampsia is unknown but is suspected to be involved with
immune activation in some cases. The maternal immune system can recognize an allogenic fetus or be ignited by cell damage due to placental hypoxia (Conrad & Benyo, 1997; Pennington, Schlitt, Jackson, Schulz, & Schust, 2012). In the latter case, it is also possible that placental hypoxia and damage is secondary to hypertension.

In a systematic review with meta-analysis of several publications, Lau et al found that preeclampsia is associated with elevated maternal circulating levels of pro-inflammatory cytokines such as Il-6 and TNF-α (Lau et al., 2013). Paradoxically, the same study found elevated anti-inflammatory Il-10 in maternal circulation. Additionally, inflammatory cytokines such as TNF-α are not only found in maternal circulation during preeclampsia but are also found at elevated levels in amniotic fluid, directly exposing the fetus to these factors (Kupferminc, Peaceman, Wigton, Rehnberg, & Socol, 1994). Therefore, in a pregnancy complicated by preeclampsia, a developing fetal brain can be exposed to elevated cytokine levels associated with aberrant brain development and behavioral abnormalities in mouse models of autism and schizophrenia.

While some studies have shown that obstetric complications are associated with a 2.2 times increase in relative risk of schizophrenia, these studies do not address whether hypoxia, immunological factors, or a combination are responsible for the increased tendency towards developing schizophrenia (Dalman C, Allebeck P, Cullberg J, Grunewald C, & Köster M, 1999). Meta analysis of several studies has also found a significant increase in schizophrenia incidence after preeclampsia exposure, but these analyses have also been descriptive rather than informative of the actual cause of increased schizophrenia risk (Cannon, Jones, & Murray, 2002). Further study of the
mediators of aberrant development will be needed to understand how obstetric complications give rise to the pathologies of schizophrenia and autism. Moreover, a better understanding of the mechanisms behind altered development can lead to future therapies.
Specific Aims and Objectives

Previous studies have demonstrated that the *in utero* immune environment can adversely affect fetal brain development. Additionally, several studies have established that preeclampsia is associated with elevated pro-inflammatory cytokines in maternal circulation and amniotic fluid. Because of the lack of evidence for preeclampsia playing a causative role in the outcome of schizophrenia and autism, we seek to better characterize the role of immunology in these disorders.

The specific aims of the study are:

1. To establish that environmental factors contribute significantly to the risk of developing schizophrenia and autism.
2. To review the literature investigating the relationship between pregnancies complicated by preeclampsia and the risk of schizophrenia and autism.
3. To suggest further characterization of the specific events that may lead to abnormal brain development and mental illness after exposure to the immune environment caused by preeclampsia.
4. To discuss the possible reasons for the differences in symptoms and pathology for ASD and schizophrenia given their similar etiologies.

We hypothesize that there will be a greater incidence of schizophrenia and ASD in offspring of women who experienced preeclampsia and immune activation during their pregnancy with those offspring compared to those that do not show these markers.
1. Genes Vs Environment

1.1 Autism

Many neuropsychiatric and developmental disorders have complicated etiologies that are not entirely explained by genetics alone. In the cases of schizophrenia and ASD, twin studies have confirmed evidence from family and population studies that both genetic inheritance and environmental factors contribute as risk factors to some extent. As the scientific understanding of both of these disorders has evolved over the last 20 years, twin studies continue to investigate and predicted heritability given new diagnostic parameters. Despite the fact that the rarity of these disorders renders many of these studies underpowered, twin studies are useful in establishing a baseline estimate of heritability.

While ASD runs in families and is more prevalent in males than females (4:1), there is no established genetic cause for most cases of this disorder. Despite the lack of clearly responsible genes, early family studies reported high genetic heritability (about 90%) for ASD. However, recruitment of subjects for these studies was not limited to validated cases of ASD by current standards. To replicate the environmental stressors associated with having a disabled sibling, contemporary studies also include control families in which one child has Down’s syndrome (Bolton et al., 1994; Pickles et al., 2000). Family history from 99 autistic and 36 Down’s syndrome probands found a higher familial loading for autism (2.9%) compared to Down’s syndrome (0%). A larger study surveying 3,095 first or second-degree relatives of 185 families (149 with a child with ASD) found a familial loading of 2.9% compared to the general population of 0.5%.
autism and 36 control families with a child with down syndrome), also confirmed an increased risk of autism among relatives of those with the disorder (Pickles et al., 2000). However, the expression patterns within these families did not reflect x-linked inheritance nor imprinted x-linked inheritance, suggesting ASD is a heterogeneous disorder caused by many factors (Pickles et al., 2000).

Confirming a role for both environment and genetics, an early twin study reported a 36% concordance rate for ASD in monozygotic twins and a 0% concordance for dizygotic pairs (Folstein & Rutter, 1977). However, the representative group was of limited size with only 21 same-sexed twin pairs, 11 being monozygotic and 10 dizygotic. All twin pairs had one child with ASD, however recruitment of subjects did not exclude those exposed to biological hazards that could cause brain injury in utero. Of the 17 pairs discordant for autism, 12 may have been exposed to brain damage due to biological hazards such as a pathologically narrow umbilical cord, neonatal apnea, low birth weight, or encephalitis. This finding suggested that in addition to genetic risk factors, perinatal exposure to biological hazards predisposes a child to developing ASD. A larger, more recent twin study conducted in 47 monozygotic and 41 dizygotic pairs with validated cases of ASD found a much smaller difference in concordance between monozygotic and dizygotic twins, suggesting a greater role for environment in the etiology of ASD that previously thought (Hallmayer, 2011). Concordance in male twins with ASD was 0.58 for 40 monozygotic pairs (95% CI, 0.42-0.74) and 0.21 for 31 dizygotic pairs (95% CI, 0.09-0.43). Despite the higher prevalence of ASD in males, twin pairs of both sexes yielded consistent trends in concordance in with the concordance for females being 0.60
for 7 monozygotic pairs (95% CI, 0.28-0.90) and 0.27 for 10 dizygotic pairs (95% CI, 0.09-0.69). In contrast to earlier studies, this investigation concluded that the genetic heritability for autism is 37% (95% CI, 8%-84%) while shared environmental factors contribute 55% (95% CI, 9%-81%) of liability (Hallmayer, 2011). The disparity in concordance between monozygotic and dizygotic twin pairs is indicative of the influence of prenatal factors to the risk of disease. While monozygotic concordance is higher, dizygotic concordance is greater than previously predicted, leaving room for in utero environment to impact disease risk. The incomplete concordance for monozygotic twins also is also evidence that environmental factors play a role.

1.2 Schizophrenia

Schizophrenia is a neuropsychiatric disorder with a high estimated heritability ranging from 83-87% (Cardno & Gottesman, 2000). Twin studies have illuminated the extent to which genetic contributions impact the risk of developing schizophrenia. A Danish based study conducted in 44 twin pairs used contemporary diagnostic criteria for schizophrenia to measure concordance rates in 13 monozygotic and 31 dizygotic twins. Using ICD-10 criteria, concordance was 44% for monozygotic pairs and 3% in dizygotic pairs (Klaning, 2015). Similar concordance rates have been reported for monozygotic pairs in previous studies using older diagnostic criteria. The criteria and populations used in these studies are summarized in Table 2. While there are consistent findings for the concordance rate in monozygotic twins, there is more variability for dizygotic twins. This raises many questions about the impact of shared prenatal environments on schizophrenia.
risk. Also, two-thirds of monozygotic twins share a placenta, which is a major environmental factor not accounted for in these calculations for genetic heritability (Patterson, 2007).

Table 2. Concordance Rates for Schizophrenia from Twin Studies.
Twin studies conducted in different countries using different diagnostic criteria for schizophrenia have found similar concordance rates for monozygotic twins. Adjusted from Cardno et al. to include only schizophrenia.

<table>
<thead>
<tr>
<th>Authors</th>
<th>Country</th>
<th>Ascertainment</th>
<th>Diagnostic Criteria</th>
<th>N of pairs and concordance</th>
<th>Heritability Estimate (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Klahn et al.</td>
<td>Denmark</td>
<td>Population register</td>
<td>ICD-10</td>
<td>13 (44%) 17 (11%)</td>
<td></td>
</tr>
<tr>
<td>Cannon et al.</td>
<td>Finland</td>
<td>Population register</td>
<td>ICD-8, DSM-III-R after 1987</td>
<td>67 (46%) 186 (9%)</td>
<td>83% (75, 89)</td>
</tr>
<tr>
<td>Tsujita et al.</td>
<td>Japan</td>
<td>Hospital admissions</td>
<td>DSM-III-R</td>
<td>18 (50%) 7 (14%)</td>
<td></td>
</tr>
<tr>
<td>Cardno et al.</td>
<td>UK</td>
<td>Hospital register</td>
<td>RDC</td>
<td>42 (41%) 56 (5%)</td>
<td>82% (71, 90)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>DSM-III-R</td>
<td>40 (43%) 50 (0%)</td>
<td>84% (19, 92)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>ICD-10</td>
<td>43 (42%) 50 (2%)</td>
<td>83% (7, 91)</td>
</tr>
</tbody>
</table>

MZ, monozygotic; DZ, same sex dizygotic

Because Schizophrenia is unlike autism, in that it is generally diagnosed in adulthood, the role of pre-natal environmental risks are not clearly represented by concordance rates in twins. Because of relatively later diagnosis, the concordance rate in twins is a reflection of both prenatal and postnatal factors, rather than genetic factors alone. While the concordance rate of less that fifty percent indicated that schizophrenia is not entirely due to genetic causes, whether environmental factors contribute to risk
prenatally or prenatally is not clear. According to the “neurodevelopmental hypothesis” of schizophrenia, environmental factors harm the developing brain, manifesting as neuropsychiatric symptoms later in life.

2. Preeclampsia and Prenatal Environmental Risk Factors

2.1 Preeclampsia

During pregnancy, fetal cytotrophoblast cells acquire endothelial morphology and invade maternal endometrial spiral arteries at the implantation site (Pennington et al., 2012). After enmeshing with maternal endothelial cells in the artery walls, the vessel becomes “leaky,” permitting maternal blood to fill the intervillous spaces of the placenta. In preeclampsia, there is incomplete remodeling of the spiral arteries by fetal cells and blood flow is impaired. Doppler ultrasound studies confirm impaired placental perfusion and incomplete vascular remodeling (Aquilina & Harrington, 1996). While endovascular remodeling occurs as 9 weeks of gestation and placental perfusion begins at 10-12 weeks, preeclampsia can not be diagnosed until 20 weeks (Caniggia, Winter, Lye, & Post, 2000). It is unclear if vascular abnormalities are a cause of preeclampsia or another symptom of an underlying issue that also leads to preeclampsia.
Figure 1. Preeclampsia as a Multifactorial Disease.
Genetics and environment may synergistically contribute as risk factors for developing preeclampsia. Preexisting immune dysfunction can compound inflammation that will expose the developing fetus to cytokines known to alter brain development.
2.2 Preeclampsia as a Risk Factor

The relationship between obstetric complications and psychiatric disorders is a well-studied topic that has contributed support to the developmental model of schizophrenia. Some of the strongest evidence for an elevated risk of schizophrenia following in utero exposure to preeclampsia comes from a longitudinal study of the Swedish National Birth Cohort by Dalman et al. (Dalman C et al., 1999). Follow-up was performed on 507,516 children born between 1973 and 1977 with a diagnosis of schizophrenia between 1987 and 1995. There were 238 cases of schizophrenia as measured by the IDC9 (41.6% female) and 507,278 controls. Adjustments were made for maternal age, year of birth, maternal history of psychosis, marital status. Preeclampsia was associated with a relative risk of 2.5 (95% CI 1.4-4.5) and was also the only obstetric complication found to have a significant increase of risk.

While Dalman et al. used a large cohort, meta-analysis performed on several studies can provide a more reliable view on prenatal risk factors. Including Dalman et al, six studies were utilized to perform a meta-analytical review of preeclampsia as a risk factor for schizophrenia (Cannon et al., 2002). In total, there were 1,720 participants with schizophrenia, of which 75 had preeclampsia exposure, and 510,275 control subjects of which 18,289 has preeclampsia exposure. Preeclampsia was associated with a slightly elevated risk of schizophrenia (odds ratio of 1.36 and 95% CI of 0.99 to 1.85, \( p=0.05 \)), however this risk was much lower than that previously reported by Dalman et al. With an
odds ratio less than two according to this meta-analysis, the risk posted by preeclampsia is controversial, but not without support.

A more recent study published after this meta-analytic review also reported a higher relative risk for schizophrenia after preeclampsia exposure. In this Danish nested-case control study, information was collected from the Danish Psychiatric National Register on 227 individuals with schizophrenia and 5,416 matched controls. Diagnoses for schizophrenia were made with the ICD-8 or ICD-9 guidelines. After adjusting for familial psychiatric history, socio-economic status and demographic factors, schizophrenia was associated with preeclampsia with an incidence rate ratio of 2.72 (95% CI 1.0-7.3). However, only five of the schizophrenic individuals had been exposed to preeclampsia. Like previous studies comparing the overlap of multiple rare diseases, this investigation also lacks sufficient breadth and sample size to be conclusive. With variability in the reported odds ratio for the risk of schizophrenia after preeclampsia exposure, more studies focusing on this issue would be valuable to establish a relationship between these two disorders. Also, as the last meta-analysis on schizophrenia and obstetric complications was published over ten years ago, a new review of contemporary publications, with a focus on preeclampsia, is also in need.

The early onset of symptoms and pathology of ASD suggest that the etiology if this disorder is linked to neurodevelopment and events that occur in utero. The first meta-analytic review on obstetric complications and ASD was performed by Gardener et al and revealed no significant increase in risk of ASD with preeclampsia exposure (effect estimate of 1.01 and 95% CI of 0.8-1.27) (Gardener, Spiegelman, & Buka, 2009). This
review utilized 25 publications on preeclampsia and ASD published prior to 2007. However, these studies were not screened for methodological strength, results from the included studies were not weighted for quality and several did not use current operational criteria for ASD. While broad inclusion criteria maximize the data available for analysis, quality control and reliability can be compromised. These shortcomings necessitated the subsequent meta-analytic review by Guinchat et al. on studies published after March 2007 (Guinchat et al., 2012). Of the studies eligible for analysis, four reported significant results for preeclampsia as a risk factor with effect estimates between 1.49 and 1.69. Moreover, a very recent population-based case-control study using the Childhood Autism Risk from Genetics and Environment (CHARGE) cohort reported evidence of preeclampsia as a risk factor for ASD (Walker CK et al., 2015). In a group of 517 individuals with ASD and 350 typically developing controls, an elevated risk of ASD was found to be associated with exposure to preeclampsia (adjusted odds ratio of 2.36; 95% CI, 1.18-4.68) and severe preeclampsia (adjusted odds ratio of 2.29; 95% CI, 0.97-5.43). Given the trend in recent literature, an updated and rigorous meta-analytic review on studies employing contemporary diagnostic criteria for ASD would be valuable in illuminating the role of preeclampsia as a risk factor in pervasive development. While recent publications present strong evidence for elevated risk of ASD with preeclampsia, these studies fail to include measurements of clinical parameters such as cytokines or hormones in either the mother or fetus that can point to causation.
2.3 Preeclampsia and Inflammation

While preeclampsia is a multifactorial disease with multiple etiologies, there is some evidence to suggest that a subgroup of cases may be related to underlying maternal immune irregularities (Duckitt & Harrington, 2005). In a systematic review of controlled studies, Duckett and Harrington reported that preexisting autoimmune disorders are a risk factor for preeclampsia (relative risk 6.9, 1.1 to 42.3). Two cohort studies in this review also reported a greater relative risk for developing preeclampsia in women who have antiphospholipid antibodies such as anticardiolipin antibody or lupus anticoagulant. In addition to autoimmune induced inflammation, irregularities in anti-inflammatory mechanisms are also associated with preeclampsia. IL-10 is an anti-inflammatory cytokine that contributes to fetal allograft tolerance (Makris, Xu, Yu, Thornton, & Hennessy, 2006). Significant reduction in placental mRNA expression of IL-10 was reported in women with preeclampsia compared to controls (p=0.015, n=43) (Makris et al., 2006). This difference in placental mRNA expression was associated with an IL-10 promoter polymorphism.

Further evidence for an immune component to preeclampsia has come from studies on monocytes, the immune cells responsible for triggering inflammation. A recent study found that monocytes isolated from women with preeclampsia (n=85) express more pro-inflammatory markers (M1 activation) than those of normotensive women (n=52) (Medeiros et al., 2014). The presence of more M1 activated monocytes causes systemic inflammation, either as a symptom of preeclampsia, or as a cause of it. The same study confirmed lower synthesis of anti-inflammatory IL-10 by monocytes from
preeclamptic women in vitro. M1 polarization of macrophages and lower IL-10 production was consistent in both early- and late-onset preeclampsia.

Without the presence of an underlying immune disorder, the pathogenesis of preeclampsia may itself cause secondary inflammation. Regardless of the precipitating event, high blood pressure and irregular cytотrophoblast invasion of placental arteries results in vascular damage (Pennington et al., 2012). Trophoblastic cell death in the placenta may release paternal antigens and induce the maternal immune system to respond with inflammation (Johansen, Redman, Wilkins, & Sargent, 1999). There are more trophoblastic cells and cell fragments in the uterine vein blood, but not in peripheral blood, of women with preeclampsia compared to controls (p<0.05, n=38). Another possible result of incomplete remodeling of spiral arteries is vascular instability and hypoxia-reperfusion injury. As blood flows through these high resistance vessels, the lack of trophoblastic invasion renders the vessels non-vasoactive, causing intermittent hypoxia followed by normoxia. Hypoxia-reperfusion injury is associated with an increase in pro-inflammatory TNF-α production by the placenta (Hung, Skepper, & Burton, 2001).

There is abundant literature comparing cytokine levels in preeclamptic and normotensive women. A selection of case-control studies measuring cytokine levels is summarized in Table 3. Both placental and plasma inflammatory cytokines have been shown to be elevated in pregnancies complicated by preeclampsia by different studies.
The abundance of literature on this topic precludes variability in study design and quality with some studies failing to use proper control parameters (Wang & Walsh, 1996) and others being underpowered (Benyo, Smarason, Redman, Sims, & Conrad, 2001). A systematic meta-analysis by Lau et al. is therefore useful in determining consensus and discordance in the literature (Lau et al., 2013). Unlike previous reports, this study includes separate analysis on severe vs. mild preeclampsia as well as early vs. late onset of the disease. Studies were also subcategorized by trimester to provide data beyond only the third trimester. Moreover, cytokine levels in human plasma are physiologically unlikely to be at or near zero, making their distribution non-normal. In contrast to

<table>
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<tr>
<th>Study</th>
<th>Parameters</th>
<th>Control</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kupferminc et al (1994)</td>
<td>Severe preeclampsia n=21, pregnant control n=26</td>
<td>parity, gestational age; uneventful term pregnancies</td>
<td>Increased plasma and amniotic TNF-α in patients with PE*</td>
</tr>
<tr>
<td>Wang and Walsh (1996)</td>
<td>Pre-eclampsia n=11; pregnant control n=15</td>
<td></td>
<td>Increased placental TNF-α protein concentration and mRNA in patients with PE</td>
</tr>
<tr>
<td>Vince et al (1995)</td>
<td>Pre-eclampsia n=31; pregnant control n=31</td>
<td>Age, parity, gestational age</td>
<td>Increased IL-6, TNF-α, and soluble TNF-R in patients with PE</td>
</tr>
<tr>
<td>Benyo et al (2001)</td>
<td>Preeclampsia n=8, control pregnant women n=8</td>
<td>Cesarean section</td>
<td>Increased circulating TNF-α, but no change in placental cytokine levels in patients with PE</td>
</tr>
</tbody>
</table>

*PE, preeclampsia
previous meta-analyses, this study employs non-parametric statistics to account for non-normally distributed cytokine levels in the population.

Surveying twenty-three studies with a total of 1,015 women with preeclampsia and 925 normotensive women, Lau et al. found that circulating TNF-α is higher in preeclamptic women. The mean difference in TNF-α levels was 8.11 pg/mL (95% CI 5.87-10.34 pg/mL). In thirteen studies comprising 425 preeclamptic women and 363 normotensive pregnant women, maternal circulating IL-6 was found to be significantly higher in women with preeclampsia. The mean difference was 7.96 pg/mL (95% CI 2.65-13.28 pg/mL). After analyzing data according to trimester, it was found that in the third trimester, preeclamptic women had higher TNF-α and IL-6 compared to controls. There was, however, insufficient evidence to confirm these phenomena in first and second trimester pregnancies. There was insufficient data to perform analysis based on early or late onset preeclampsia.

**Figure 2. Meta-analysis of IL-6 Levels in Women with Preeclampsia.** Taken from Lau et al.

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Preeclampsia Mean [pg/mL]</th>
<th>StDev [pg/mL]</th>
<th>Total</th>
<th>Normotensive Mean [pg/mL]</th>
<th>StDev [pg/mL]</th>
<th>Total</th>
<th>Weight</th>
<th>Mean Difference [pg/mL]</th>
<th>95% CI [pg/mL]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shamaa 2011</td>
<td>81.65</td>
<td>1.511</td>
<td>330</td>
<td>97.6</td>
<td>1.427</td>
<td>260</td>
<td>65.00</td>
<td>-5.35</td>
<td>-8.97, -1.72</td>
</tr>
<tr>
<td>Chekrou 2009</td>
<td>85.60</td>
<td>29.98</td>
<td>29</td>
<td>87.9</td>
<td>17.32</td>
<td>29</td>
<td>0.1%</td>
<td>-4.50</td>
<td>-9.66, 0.67</td>
</tr>
<tr>
<td>Snip 2010</td>
<td>278.00</td>
<td>223.35</td>
<td>50</td>
<td>45</td>
<td>16.976</td>
<td>50</td>
<td>6.1%</td>
<td>-222.00</td>
<td>168.91, 294.00</td>
</tr>
<tr>
<td>Antin-Hayeuse 2003</td>
<td>191.02</td>
<td>55.3203</td>
<td>20</td>
<td>59.7</td>
<td>6.478</td>
<td>18</td>
<td>0.7%</td>
<td>131.27</td>
<td>106.83, 155.71</td>
</tr>
<tr>
<td>Sharma 2007</td>
<td>147.2</td>
<td>46.42</td>
<td>54</td>
<td>11.2</td>
<td>5.46</td>
<td>50</td>
<td>0.6%</td>
<td>136.00</td>
<td>112.86, 159.11</td>
</tr>
<tr>
<td>Masenini 2005</td>
<td>87.66</td>
<td>6.83</td>
<td>30</td>
<td>9.3</td>
<td>0.56</td>
<td>19</td>
<td>0.9%</td>
<td>55.26</td>
<td>36.23, 80.48</td>
</tr>
<tr>
<td>Alfiwe 2005</td>
<td>53.8</td>
<td>30</td>
<td>24</td>
<td>33.8</td>
<td>33.8</td>
<td>18</td>
<td>1.1%</td>
<td>20.00</td>
<td>31.69, 8.90</td>
</tr>
<tr>
<td>Orun 2004 (mild)</td>
<td>196.60</td>
<td>190</td>
<td>130</td>
<td>21</td>
<td>30</td>
<td>15</td>
<td>1.8%</td>
<td>36.00</td>
<td>19.63, 52.17</td>
</tr>
<tr>
<td>Manni 1999</td>
<td>26</td>
<td>19.6</td>
<td>16</td>
<td>22.8</td>
<td>12.8</td>
<td>16</td>
<td>2.5%</td>
<td>3.40</td>
<td>-5.07, 14.87</td>
</tr>
<tr>
<td>Nyeve 2006</td>
<td>14.53</td>
<td>13.5</td>
<td>25</td>
<td>17.3</td>
<td>11</td>
<td>25</td>
<td>4.3%</td>
<td>-3.07</td>
<td>-4.50, 4.18</td>
</tr>
<tr>
<td>Shahrooger 2007 (26 weeks)</td>
<td>29.43</td>
<td>12.16</td>
<td>30</td>
<td>9.72</td>
<td>6.35</td>
<td>30</td>
<td>6.4%</td>
<td>10.71</td>
<td>6.40, 15.62</td>
</tr>
<tr>
<td>Cenikoff 2003 (mild)</td>
<td>95.50</td>
<td>9.5</td>
<td>20</td>
<td>32.8</td>
<td>6.3</td>
<td>21</td>
<td>5.5%</td>
<td>23.70</td>
<td>19.10, 28.30</td>
</tr>
<tr>
<td>Trison 2001</td>
<td>15.90</td>
<td>5.67</td>
<td>24</td>
<td>6.95</td>
<td>7.61</td>
<td>19</td>
<td>5.0%</td>
<td>4.90</td>
<td>5.67, 12.62</td>
</tr>
<tr>
<td>Teram 2003</td>
<td>15.74</td>
<td>5.05</td>
<td>8.31</td>
<td>6.55</td>
<td>6.48</td>
<td>8.31</td>
<td>6.6%</td>
<td>23.74</td>
<td>5.36, 9.58</td>
</tr>
<tr>
<td>Koygat 2004</td>
<td>16.3</td>
<td>4.78</td>
<td>45</td>
<td>3.033</td>
<td>2.45</td>
<td>30</td>
<td>7.0%</td>
<td>12.70</td>
<td>11.05, 14.35</td>
</tr>
<tr>
<td>Ounis 2008</td>
<td>18.47</td>
<td>4.17</td>
<td>53</td>
<td>8.86</td>
<td>3.19</td>
<td>20</td>
<td>7.1%</td>
<td>9.65</td>
<td>8.33, 10.98</td>
</tr>
<tr>
<td>Ruchan 2009 (mild)</td>
<td>2.89</td>
<td>1.92</td>
<td>17</td>
<td>3.18</td>
<td>3.99</td>
<td>17</td>
<td>7.1%</td>
<td>-0.89</td>
<td>-1.79, 0.91</td>
</tr>
<tr>
<td>Freeman 2004</td>
<td>2.23</td>
<td>2.19</td>
<td>45</td>
<td>2.73</td>
<td>3.44</td>
<td>44</td>
<td>7.1%</td>
<td>-0.50</td>
<td>-1.59, 0.59</td>
</tr>
<tr>
<td>Sarm 2002</td>
<td>11.1</td>
<td>1.4</td>
<td>10</td>
<td>9.2</td>
<td>0.8</td>
<td>80</td>
<td>7.2%</td>
<td>1.90</td>
<td>0.61, 3.19</td>
</tr>
<tr>
<td>Negan 2009</td>
<td>14.17</td>
<td>0.66</td>
<td>25</td>
<td>17.09</td>
<td>1.56</td>
<td>25</td>
<td>7.2%</td>
<td>-3.42</td>
<td>-4.08, -2.75</td>
</tr>
<tr>
<td>Yonezuma 2002 (mild)</td>
<td>2.98</td>
<td>1.37</td>
<td>21</td>
<td>2.4033</td>
<td>2.11</td>
<td>21</td>
<td>7.2%</td>
<td>0.00</td>
<td>0.38, 1.15</td>
</tr>
<tr>
<td>Genov 2009 (mild)</td>
<td>1.84</td>
<td>1.60</td>
<td>91</td>
<td>1.39</td>
<td>1.0971</td>
<td>60</td>
<td>7.2%</td>
<td>0.49</td>
<td>0.11, 1.10</td>
</tr>
<tr>
<td>Purcell 2008</td>
<td>1.32</td>
<td>1.01</td>
<td>61</td>
<td>1.0494</td>
<td>0.62</td>
<td>62</td>
<td>7.3%</td>
<td>0.52</td>
<td>-0.33, 0.87</td>
</tr>
</tbody>
</table>

Total (95% CI) 1615 925 100.0% 8.11 5.87, 10.34

Heterogeneity: Tau² = 17.96, Chi² = 1330.81, df = 22 (P < 0.0001); I² = 98%
Test for overall effect: Z = 7.11 (P = 0.0001)

Higher in normotensive
Higher in preeclampsia
While studies previously reviewed in this paper have reported lower expression of the anti-inflammatory cytokine IL-10 in women with preeclampsia (Makris et al., 2006; Medeiros et al., 2014), the results of meta-analysis by Lau et al. found elevated IL-10 in preeclamptic women (Lau et al., 2013). The meta-analysis, however, was performed using only papers reporting elevated IL-10 rather than using a weighted average of studies with different outcomes. Given the consistency of findings on elevated pro-inflammatory cytokines in women with preeclampsia, lower IL-10 expression would be more consistent with the immune state described by other findings. Further in-depth study on this issue and a more comprehensive meta-analysis is required to better understand the role of IL-10 in the preeclamptic immune environment.

2.4 Neuroinflammation in Neurodevelopmental Disorders

The effect of neuroinflammation on neurdevelopment has long been studied in the context of infectious disease. The Prenatal Determinant of Schizophrenia (PDS) was a prospective study based on a cohort of 20,000 pregnant women in Northern California, from which samples of sera were collected during prenatal visits (Opler & Susser, 2005). This study was unique in that prenatal infection was confirmed with serological measures of anti-influenza antibodies. A seven-fold increase in the risk of schizophrenia and schizophrenia spectrum disorders (SSD) was found in individuals with influenza exposure during the first trimester. However, developmental abnormalities are associated with various prenatal infections, rather than one specific pathogen. Rubella, toxoplasma gondii, measles, polio, herpes simples, and genital infections during pregnancy have also
been associated with increased risk of developmental disorders in offspring (Meyer, Feldon, & Yee, 2009). This suggests that the immune response, which is common to all of these infections, may be the mediator of developmental changes, rather than the infectious agents, themselves. The pro-inflammatory cytokines induced by such infections may alter brain development leading to schizophrenia and autism.

This hypothesis is supported by studies performed on mouse models of autism and schizophrenia. The core symptoms of autism such as repetitive behavior and reduced social behavior have been produced in mice using the maternal immune activation (MIA) model of autism. In this model, injecting pregnant mice with an immunogenic compound such as virus, bacterial lipopolysaccharide (LPS), or double-stranded RNA (poly (I:C)). Offspring born to pregnant mothers inject with poly (I:C)) showed behavioral abnormalities. Mice emit USVs as pups to communicate with their mothers and as adults in response to mates or other mice. MIA offspring made fewer ultrasonic vocalizations (USVs) during both childhood and adulthood. These USVs were also harmonically and qualitatively different from those of control mice. Marble burring is a test of repetitive behavior in which mice are observed burring a field of marbles into cage bedding. MIA offspring also displayed increased marble burring behavior, consistent with autistic trains in humans. Self-grooming is also used as an index of repetitive behavior and was observed to be increased in MIA offspring.

The MIA model is also relevant to schizophrenia. Using the MIA model, Shi et al. infected pregnant mice at day 9.5 (mid-pregnancy) with influenza virus and measured behavioral abnormalities in the offspring (Shi, Fatemi, Sidwell, & Patterson, 2003). Mice
with prenatal influenza exposure displayed abnormal behaviors consistent with mouse models of autism and schizophrenia such as deficiencies in prepulse inhibition (PPI), social interactions, and exploratory behavior in open field and novel-object tests. The abnormal behavior was ascribed to the immune reaction to the virus as influenza does not spread beyond the lung and no viral particles were found in histological preparations of mouse brains. Furthermore, PPI deficits remained when maternal injections were made with only synthetic Poly (I:C) rather than live virus. The immune system recognizes and responds to poly (I:C) even in the absence of a live virus and a deficit in PPI in the acoustic startle response is one of the hallmarks of schizophrenia in mouse models of the disease.

The immune reaction and subsequent developmental changes in response to poly (I:C) are mainly mediated by the inflammatory cytokine IL-6 (Smith, Li, Garbett, Mirnics, & Patterson, 2007). In fact, co-injection of poly (I:C) and anti IL-6 antibody prevents 92% of changes in gene expression in the brains of offspring exposed to the challenge. Additionally, IL-6 KO mice injected with poly (I:C) show no behavioral deficits after pre-natal antigen exposure. While these studies were conducted in a mouse model, human studies have also suggested a relationship between elevated immune response and schizophrenia.
Table 4. The Relationship Between Prenatal Immune Challenge and Mental Illness.
Schizophrenia and related disorders, such as Somatic Symptom Disorder, are associated with exposure to immune activation in utero. Adjusted from Khandaker et al (2013)(G. M. Khandaker, Zimbron, Lewis, & Jones, 2013)

<table>
<thead>
<tr>
<th>Study</th>
<th>Case/control</th>
<th>Case Definition</th>
<th>Exposure</th>
<th>Adjustment/ control</th>
<th>Main Finding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Buka et al., 2001</td>
<td>27/54</td>
<td>affective and non affective</td>
<td>IL-1b, IL-2,</td>
<td>gender, ethnicity, social class, maternal mental illness, weight gain and smoking during pregnancy</td>
<td>Increased TNF-α in case mothers; OR for psychosis 8.5 (p&lt;0.03) in offspring of women with both third trimester infection and TNF-α levels &gt;75th.</td>
</tr>
<tr>
<td>Brown et al. 2004</td>
<td>59/118</td>
<td>SSD by DSM-IV</td>
<td>IL-1β, IL-6, IL-8, TNF-α</td>
<td>Fetal age, gender, maternal age, social class, ethnicity</td>
<td>Nearly two fold increase in mean and median IL-8 at second/third trimester in case mothers</td>
</tr>
<tr>
<td>Brown et al. 2000</td>
<td>58/778</td>
<td>SSD by DSM-IV</td>
<td>Respiratory infection</td>
<td>Maternal ethnicity, education and smoking during pregnancy</td>
<td>OR SSD 2.13 (95% CI 1.05–4.35), schizophrenia 2.07 (95% CI 0.8–5.36)</td>
</tr>
<tr>
<td>Babulas et al. 2006</td>
<td>71/772</td>
<td>SSD by DSM-IV</td>
<td>Genital/reproductive infection</td>
<td>Maternal age, ethnicity, education and mental illness</td>
<td>OR SSD 5.03 (95% CI 2.00–12.64)</td>
</tr>
</tbody>
</table>

Moreover, the immunological events followed by maternal infections are not confined to the mother. Evidence from both human and mouse studies suggest that cytokines cross the placenta and enter fetal circulation where they can also cross the blood brain barrier. After performing peritoneal injections of LPS on pregnant mice, Gayle et al found elevated inflammatory cytokines in both the maternal blood and fetal amniotic fluid (Gayle et al., 2004). Previous studies using higher doses of LPS have reported elevated fetal brain cytokine production (Cai, Pan, Pang, Evans, & Rhodes, 2000; Urakubo, Jarskog, Lieberman, & Gilmore, 2001). While fetal brain cytokine mRNA levels did not change in this study, elevated stress markers were found such as corticotropin releasing hormone. Because mRNA levels reflect only production of the cytokines by the brain, and not exposure to them from circulating levels, it is possible
that cytokines reach the brain by crossing the blood brain barrier (BBB). Il-1β, TNF-α, and Il-6 cross a normal human adult and murine BBB (Dammann & Leviton, 1997). The BBB is also thought to be more permeable in the fetus compared to adults (Dammann & Leviton, 1997). Additionally, pro-inflammatory cytokines, themselves increase BBB permeability, leading to even greater likelihood that these compounds reach and alter the developing brain.

3. Neuroimmunology and Development: Mechanisms

How cytokines impart the developmental changes or brain damage associated with psychiatric disorders is still not well understood. Several different roles have been found for cytokines in neural plasticity and differentiation. Glia are responsible for various aspects of brain development from neuronal migration to modulation of precursor cell growth and differentiation (Stolp, 2013). Microglia are the resident macrophages of the CNS, become active in response to circulating inflammatory cytokines, and are responsible for immune functions such as phagocytosis and additional cytokine production. Cytokines produced by microglia modulate differentiation of neural progenitor cells. Using neutralizing antibodies and recombinant cytokines, Nakashini et al. showed that Il-6 is essential for the induction of astrocyte differentiation and can accordingly shift the glial population when elevated (Nakanishi et al., 2007). TNF-α also induced astrocyte differentiation (Whitney, Eidem, Peng, Huang, & Zheng, 2009). Astrocytes are responsible for neuronal differentiation, causing two-fold increase in neural stem proliferation and tenfold rate of differentiation in co-cultures (Whitney et al.,
2009). Altering temporal regulation of astrocyte production due to acute inflammation may disrupt normal brain development.

Both IL-6 and TNF-α have also been shown to inhibit neuronal differentiation in the hippocampus (Liu, Lin, & Tzeng, 2005; Vallières, Campbell, Gage, & Sawchenko, 2002). IL-6 produced by microglia decreases neuronal differentiation by 50% in cell culture models, and this effect is loss with treatment of anti IL-6 antibody (Whitney et al., 2009). The effect of TNF-α on neuronal differentiation and survival is less clear. Activated microglia expressing TNF-α prevented neuronal differentiation in cell culture studies. Furthermore, blocking TNF-α action with soluble receptors or the inhibitor pentoxyfylline was somewhat effective in rescuing neuronal differentiation. However, other studies report no initial loss of neural differentiation with TNF-α treatment. These differences in experimental outcomes may be accounted for by differences in techniques and the models being used. The length of exposure to TNF-α as well as differential expression of receptor subtypes may also be relevant.

Overexpression of microglial IL-1β and IL-6 due to inflammation exposure in utero has also been associated with altered glutaminergic synapses in adult mice (Roumier et al., 2008). Furthermore, TNF-α increases synaptic activity in rat hippocampal slices in vitro, which can lead to altered brain development and behavior (Grassi et al., 1994). In a rat study, a synthetic, highly active fusion protein of IL-6 increased neurotrophins (NT) of the nerve growth factors (NGF) family (März, Heese, Dimitriades-Schmutz, Rose-John, & Otten, 1999). NGFs influence synaptic strength, which can lead to altered cognition (Nawa, Takahashi, & Patterson, 2000). These neuroprotective NGFs were induced
differentially throughout the brain and had the greatest effect in the hippocampus, cortex and cerebellum (März et al., 1999).

Brain derived neurotropic factor (BDNF) is the main regulator of neuronal survival, differentiation and synapse maturation (Heese, Hock, & Otten, 1998). Inflammatory cytokines such as Il-1 and NGF suppress BDNF expression while Il-6 enhances its expression (Nawa et al., 2000). Differential modulation of BDNF in various brain regions by multiple cytokines can have global effects on cognition and development. The molecules regulated by BDNF are also altered in schizophrenia. Examples of this include somatostatin, calbindin D, TH/ Dopamine, synaptophysin, and CCK, among others (Nawa et al., 2000). Somatostatin induces the inhibitory action of the dorsolateral prefrontal cortex, which is abnormally active in schizophrenia (Morris, Hashimoto, & Lewis, 2008). Reduced calbindin-positive interneurons have been reported in schizophrenia. Reducing calbindin in inhibitory interneurons reduced their excitability, leading to increased downstream disinhibition and altered cognition (Chance, Walker, & Crow, 2005).
DISCUSSION

While there is evidence supporting a developmental and immunological model for schizophrenia and autism, there is a lack of literature characterizing the circumstances that lead to the unique pathologies of these different diseases. The most obvious explanation for the differences in these diseases is that the timing of an abnormal inflammatory event can interfere with different developmental stages of the brain, thus manifesting as different symptoms. For instance, autism is more associated with cerebellar pathology than is schizophrenia. The cerebellum reaches full development relatively late in fetal life, therefore either acute inflammation in the third trimester, or chronic inflammation persistent throughout development would be able to impart cerebellar pathologies (Meyer et al., 2011). Further study of the temporal influence of inflammatory events on development and psychiatric manifestations is needed.

Alternatively, the shared aspects of schizophrenia and autism such as social deficits and altered sensory processing, may be explained by neuroinflammation in early development which may either persist leading to one disease or resolve leading to the other disease. The outcome and course of neuroinflammation may be determined by either additional environmental factors such as access to healthcare or other obstetric complications, or by genetic susceptibility to immune disorders. Failing to responding to an acute inflammatory event with sufficient anti-inflammatory measures may be a result of genetic background (Figure 3). Genes contributing to the risk of preeclampsia may also modulate the severity of the inflammatory exposure in utero. The difficulty in tracing
these subtle contributing factors in is the lack of a sufficient study size to be able to capture rare genetic susceptibilities or alternative environmental factors.

**Figure 3. Immune profiles in Schizophrenia and Autism.**
Taken from Meyer et al 2011 (Meyer et al., 2011) Like maternal infection, preeclampsia initiates acute inflammation in the fetal environment. The persistence or suppression of inflammation may rely on genetic factors, which differentiate the outcomes of schizophrenia and autism by modulating latent versus chronic neuroinflammation. The acute inflammatory event, however, is present in both cases and may account for shared attributes between both disorders.

In their review of the neuroimmunology of developmental disorders, Meyer et al. put forth a hypothesis that the pathologies of schizophrenia and autism are shaped by latent inflammation and chronic inflammation, respectively, and that the course of either immunological profile is determined by differences in genetics (Meyer et al., 2011).
There is evidence that prenatal immune challenge can lead to permanent alterations in cytokine production and immune reactivity. Offspring of pregnant mice injected with poly (I:C) have elevated brain cytokine levels from birth to adulthood (Garay, Hsiao, Patterson, & McAllister, 2013). Moreover, these elevations are region-specific and coincide with areas known to be abnormal in schizophrenia and autism. While both IL-1β and IL-10 (Il-6 is elevated, but p=0.09) are elevated at birth, Il-6 and IL-10 are elevated during adulthood in the frontal cortex. In the hippocampus, Il-6 is elevated at birth, and there are persistent differences in other cytokine levels throughout development.

A theory of chronic inflammation in autism is supported by evidence from human studies. A small clinical study (n=10) reported significantly higher levels of TNF-α in the CSF of children with autism (Chez, Dowling, Patel, Khanna, & Kominsky, 2007). In support of these findings, another study using immunohistochemical techniques reported elevated glial activation in brain tissue from human subjects with autism (Vargas, Nascimbene, Krishnan, Zimmerman, & Pardo, 2005). The cerebellum, which is abnormal in autistic patients, was most notably affected by elevated inflammation. Lastly, in a case-control study, peripheral blood monocytes isolated from autistic children were found to produce higher levels of proinflammatory cytokines and lower anti-inflammatory IL-10 in response to synthetic immune stimulants (Molloy et al., 2006).

Conversely, schizophrenia is associated with higher levels of both pro- and anti-inflammatory cytokine consistent with the pathology of the latent-inflammation model. In a systematic and quantitative review of 62 studies with a total of 2,289 schizophrenic and 1,858 control individuals, Potvin et al. found that pro-inflammatory cytokines, including
IL-6, are significantly elevated in patients with schizophrenia. On the other hand, serum levels of IL-10 were found to be elevated in a subset of schizophrenics resistant to certain treatments (Maes et al., 2002). Other markers of elevated anti-inflammatory mediators have also been found in individuals with schizophrenia including the IL-1 receptor antagonist, TGF-β, and soluble TNF receptor (Meyer et al., 2011). This unique immune environment may act as a switch for the schizophrenic phenotype during development, allowing for dampened inflammation after an initial damaging acute event.
CONCLUSION

Schizophrenia and autism are disorders linked to disturbances in development. While both disorders are associated with genetic risk factors, incomplete concordance in twins suggests environmental factors are important for the development of both diseases. One well studied environmental risk factor for both schizophrenia and autism is obstetric complications. Specifically, maternal infections during pregnancy have been studied for their potential to expose a fetus to inflammatory cytokines known to modulate brain development. Preeclampsia is another obstetric complication associated with a greater risk of schizophrenia and autism in offspring. Preeclampsia ignites an immune response similar to that seen during prenatal infections and can therefore mediate neurodevelopmental changes in the same way previously studied maternal infections can.

Possible preventative therapies have been proposed, however none are in use, nor have they been tested in pregnant human populations for the purpose of preventing abnormalities in a developing fetus. Previously described experiments in mice have demonstrated that behavioral abnormalities that arrive from prenatal IL-6 exposure are ameliorated by concurrent IL-6 antibody administration (Smith et al., 2007). Because cytokines are required in normal brain development, finding appropriate situations for this therapy and proper dosage would be greatly challenging. Interferons (IFNs) are immune mediators expressed by astrocytes in response to viral challenge. Interferon-induced transmembrane-3 (IFITM3) is a necessary component of the IFN pathway and has been shown to be elevated in brains of experimental mouse models of schizophrenia...
and autism (Ibi & Yamada, 2015). Mice without IFITM3 expression are spared the alterations in neuronal and dendritic maturation seen in wild type mice after pre-natal immune challenge. Therapeutics targeting IFITM3 also have the potential to prevent brain damage, however the role of IFNs in normal brain development is not well understood. Therapies focusing on immune modulation share the common risk of disrupting normal functions of the immune system in development. Therefore, more research on the normal levels and functions of cytokines and other immune mediators in development will be needed before viable therapeutic can be developed in this class. Furthermore, determining threshold for what cytokines levels are normal or abnormal will be necessary to determine when treatment with immune suppressors is appropriate. Lastly, drug delivery will be sensitive to differences in drug availability for the other and fetus.
LIST OF JOURNAL ABBREVIATIONS

Am J Reprod Immunol ........................ American Journal of Reproductive Immunology
BMJ .................................................................BMJ: British Medical Journal
Curr Opin Cell Biol .................................. Current Opinion in Cell Biology
EMBO J ............................................................... EMBO Journal
FASEB J ............................................................. FASEB Journal
FEBS Lett ................................................................. FEBS Letters
JAMA .......................................................... JAMA: The Journal of the American Medical Association
Mol Cell Biol ........................................................... Molecular and Cellular Biology
Nat Rev Immunol .......................................................... Nature Reviews. Immunology
NEJM ............................................................. New England Journal of Medicine
PNAS Proceedings of the National Academy of Sciences of the United States of America


Expression of Inflammatory Cytokines in Placentas from Women with Preeclampsia. The Journal of Clinical Endocrinology & Metabolism, 86(6), 2505–2512. http://doi.org/10.1210/jcem.86.6.7585


Nawa, H., Takahashi, M., & Patterson, P. (2000). Cytokine and growth factor involvement in schizophrenia—support for the developmental model, 5(6). http://doi.org/10.1038/sj.mp.4000730


CURRICULUM VITAE

IDA AZIZKHANIAN
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Education

Boston University School of Medicine
M.S. Medical Sciences
September 2014-2016

New York University
B.S. in Neuroscience
September 2009-January 2013

Basic Research Experience

University of Southern California Keck School of Medicine-Yassine Lab
June, 2015-November, 2015
Research Lab Assistant
- Studied lipid metabolism in the context of Alzheimer’s disease and diabetes.
- Studied influence of metabolic syndrome on microglia function, neuroinflammation, and amyloid clearance.

California Institute of Technology-Patterson Lab
September, 2012-August, 2014
Research Lab Assistant
- Studied Rett Syndrome and effect of MeCP2 mutations on protein stability and regulation.
- Designed and carried out experiments; gave monthly presentations on progress of the project.
- Maintained cell cultures, performed immunocytochemistry, bacterial transformations, Western blot, transfections, ELISAs, and mouse brain dissections.

New York University- Klann Lab
February-August, 2012
Research Lab Assistant
- Conducted research on Fragile X Syndrome, mTOR pathway, and S6 kinase in fmr1 knock-out mice using biochemical and behavioral assays.
- Created lab reagents, conducted related assays and experiments including PCRs, statistical analysis on data from behavioral assays, gel electrophoresis,
genotyping, Western blot and their quantifications. Also had some experience handling mice for tail snipping.

Clinical and Professional Experience
Cipher Health
August-December, 2011
Intern
• Performed a variety of tasks including making sales calls to clients, making spreadsheets, performing statistical analysis on consumer data, making charts for presentation slides from said consumer data, performing research on competing companies and prospective clients

Mount Sinai Research Associates Program
September 2010-11
Research Assistant
• Screened and enrolled patients in several clinical studies and shadowed ER physicians. Trained to comply with all federal, local, FDA, IRB, and HIPAA guidelines and regulations and gained CITI certification

Activities and Leadership Experience
America Reads/ America Counts Program
September 2009- January 2010
Student Teaching Assistant
• Tutored middle school students in science and math and assisted teachers in classroom management.

Volunteer Musicians and Dancers Program
November, 2009-11
Founder and President of the Program
• Organized music and dance programs at public NYC schools; prepared and presented grant proposals to fund the program, recruited volunteer teachers, and enrolled students.
• Won $1,000 seed grant from Reynolds Youth Venture competition to fund the program