

# Prenatal and Postnatal Animal Models of Immune Activation: Relevance to a Range of Neurodevelopmental Disorders

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**ABSTRACT:** Epidemiological evidence has established links between immune activation during the prenatal or early postnatal period and increased risk of developing a range of neurodevelopmental disorders in later life. Animal models have been used to great effect to explore the ramifications of immune activation during gestation and neonatal life. A range of behavioral, neurochemical, molecular, and structural outcome measures associated with schizophrenia, autism, cerebral palsy, and epilepsy have been assessed in models of prenatal and postnatal immune activation. However, the epidemiology-driven disease-first approach taken by some studies can be limiting and, despite the wealth of data, there is a lack of consensus in the literature as to the specific dose, timing, and nature of the immunogen that results in replicable and reproducible changes related to a single disease phenotype. In this review, we

highlight a number of similarities and differences in models of prenatal and postnatal immune activation currently being used to investigate the origins of schizophrenia, autism, cerebral palsy, epilepsy, and Parkinson's disease. However, we describe a lack of synthesis not only between but also within disease-specific models. Our inability to compare the equivalency dose of immunogen used is identified as a significant yet easily remedied problem. We ask whether early life exposure to infection should be described as a disease-specific or general vulnerability factor for neurodevelopmental disorders and discuss the implications that either classification has on the design, strengths and limitations of future experiments. © 2012 Wiley Periodicals, Inc. *Develop Neurobiol* 72: 1335–1348, 2012

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## INTRODUCTION

Early life events can have significant effects on an organism's long-term health and wellbeing during adulthood. Since the "Barker hypothesis" drew attention to the impact of prenatal nutrition on the risk of subsequent adult-onset disorders such as diabetes, cardiovascular disease, and hypertension (Barker and Martyn, 1992), this field, also known as the developmental origins of health and disease, has expanded to demonstrate how influential the prenatal environment is on a

wide range of adult health outcomes (Barker, 2004; Sinclair et al., 2007; Sinclair and Singh, 2007). With respect to the central nervous system (CNS), early events that have been implicated in altering the trajectory of neurodevelopment include pregnancy and birth complications, maternal/neonatal exposures to nutritional deficiency, stress, drugs or toxins, and postnatal social deprivation (Schlotz and Phillips, 2009). Infection with resulting immune activation is another such insult, and the focus of the current article is on how animal models of prenatal and postnatal immune activation are being used to study the role of early life infection in the etiology of neurodevelopmental disorders.

Prenatal or early postnatal immune activation has been implicated in a number of major neurodevelopmental disorders, including schizophrenia, autism, cere-

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bral palsy, and epilepsy (Pakula et al., 2009; Brown and Derkits, 2010; Landrigan, 2010). While disorders like schizophrenia and autism appear to be uniquely human, certain structural, molecular, and behavioral abnormalities found in these human disorders can be assessed in animals species commonly used for preclinical research. It will be recalled that the etiologies of disorders like schizophrenia, autism, or cerebral palsy are multifactorial, likely involving a complex interplay between genetic and environmental factors. Thus, it should not be surprising if CNS effects produced by a single risk factor in isolation, like prenatal infection, are rather subtle, and may not mimic the entire spectrum of abnormalities characteristic of the disorder. Nonetheless, the development of animal models allows us to address specific questions about effects of exposure to early life infection, e.g., the timing of the critical period of exposure to the immune activation; the duration and severity of the inflammatory response; the trajectory of neurodevelopmental changes during juvenile and adult life; the mechanisms mediating effects of immune activation on neurodevelopment; and responses to potential therapeutic intervention.

The approach taken by many researchers in this area is to focus on a specific disorder and to work with a particular model of prenatal or postnatal immune activation, which attempts to mimic the epidemiology of the disorder, concentrating on assessing end points characteristic of that disorder as outcome measures. The aim of this review is to provide a brief overview of the range of models of early life immune activation currently being used within the context of various neurodevelopmental diseases. After a brief introduction to the immunogens commonly used to induce immune activation, we will describe some of the models, mainly in rodents, that are commonly used to examine effects of prenatal or postnatal immune activation in relation to schizophrenia, autism, cerebral palsy, epilepsy, and other disorders. Rather than aiming to be exhaustive, we will use a selection of examples to compare and contrast abnormalities in disease-specific endpoints observed in these models.

It is possible that a better integration of findings across specific disease-based models might enhance our understanding of the overall effects of early life exposure to infection on neurodevelopment. Therefore, in the course of the review, we hope to highlight some of the similarities and differences between these models and suggest that a broadening of the outcome measures assessed in some already well-established models or collaboration between researchers with interests in different diseases might be a valuable option to consider.

## IMMUNOGENS USED TO MODEL PRENATAL OR POSTNATAL IMMUNE ACTIVATION

### Molecular Immunogens

The most common immunogens used to induce inflammation in pregnant mice and rats are lipopolysaccharide (LPS) and polyinosinic:polycytidylic acid [poly(I:C)]. LPS, a component of the cell wall of Gram negative bacteria, is a molecular immunogen used to mimic a bacterial infection whereas poly(I:C), a synthetic, double-stranded RNA, mimics a viral infection. Both immunogens bind to toll-like receptors [LPS to TLR-4, poly(I:C) to TLR-3], initiating a signaling cascade that leads to activation of transcription factors, such as nuclear factor kappa B (NF $\kappa$ B) and subsequent transcription of genes coding for pro- and anti-inflammatory mediators such as cytokines [interleukin (IL)-1, tumor necrosis factor (TNF)- $\alpha$ , IL-6, and interferons (IFNs)], chemokines, and complement proteins. IL-6 then acts in the brain to induce cyclooxygenase-2-mediated synthesis of prostaglandins in the hypothalamus, which can mediate a fever response (Roth et al., 2009). Although there are broad similarities in some components of the proinflammatory cytokine cascade induced by both LPS and poly(I:C), there can be significant differences in the magnitude of cytokine responses induced by these two types of immunogens, as well as both quantitative and qualitative differences in the cell types that respond to activation, the profile of cytokine induction, and activation of downstream signaling cascades (e.g., Bsibsi et al., 2006; Reimer et al., 2008; Figueiredo et al., 2009). Also, importantly for models of inflammation during pregnancy, TLR3 and TLR4 may be differentially modulated by hormones, including progesterone (Jones et al., 2010), whose levels increase throughout pregnancy, peaking during late pregnancy in humans and rats and falling just before parturition in the rat (Bridges, 1984).

When comparing findings within models of early life immune activation, one simple but important factor to consider is the dosage of immunogen used. These models make widespread use of LPS as the immune activator; however, despite its frequency of use, it is difficult to compare LPS dosages across studies as it is known that the bioactivity of LPS per milligram is dependent on the lot and serotype of the strain of *Escherichia coli* (Ray et al., 1991; Akarsu and Mamuk, 2007). This results in an inability to effectively compare and contrast between models, particularly in instances where authors do not provide details of *in vivo* or *in vitro* bioactivity assays. Similar to the

case for LPS, we have recently reported that different batches of poly(I:C) obtained from the same supplier differ widely in their cytokinogenic activity when measured by induction of plasma IL-6 (Harvey and Boksa, 2012). Given this variability, the standardization of LPS and poly(I:C) dosages, through reporting of meaningful bioactivity levels in each publication, would represent a significant step forward in helping to increase the transparency and reproducibility of models of early life immune activation.

### Live Viruses

Although seemingly out of favor compared to LPS and poly(I:C), some of the first models of prenatal infection were designed using intranasal influenza administration (Shi et al., 2003). The advantage of using this immunogen is that, as the infection is live, the time course of propagation of the immune activation is naturalistic. This advantage is also a limitation, however, as the researcher loses some control over the dosing and window of exposure. Viruses have also been used in neonatal rodent models to examine the neurodevelopmental consequences of congenital or neonatal infection with specific agents such as Borna disease virus, cytomegalovirus, and lymphocytic choriomeningitis (Hornig and Lipkin, 2001; Barry et al., 2006; Bonthius and Perlman, 2007).

### Turpentine

Intramuscular injection of turpentine has an advantageous feature as a model of maternal immune activation because, in contrast to systemic LPS and poly(I:C) administration, the turpentine remains localized at the site of injection (Wusteman et al., 1990). This obviates direct effects of the immunogen on maternal organs and on the placental–fetal unit. Intramuscular turpentine causes an increase in circulating IL-6 mediated by local production of IL-1 and TNF- $\alpha$  and a robust febrile response (Luheshi et al., 1997).

### Direct Administration of Cytokines

A key question is whether activation of specific components of the immune system can account for the effects of prenatal or postnatal infection on the CNS. Models using direct administration of cytokines to pregnant rodents during gestation or to postnatal rodents have been used to address this. For example, the recognition of IL-6 as a key mediator in the inflammatory response has led to the development of

models of maternal immune activation in which IL-6 is administered directly to the pregnant dam (Samuelsson et al., 2006; Smith et al., 2007).

## DISEASE-BASED MODELS OF PRENATAL AND EARLY POSTNATAL IMMUNE ACTIVATION

### Schizophrenia

Epidemiological evidence has described an increased risk of schizophrenia in the offspring of mothers exposed to viral infections (influenza, measles, herpes simplex virus type 2, rubella, and polio), bacterial infections (pneumonia, respiratory infections, genital, and reproductive infections including bacterial vaginosis), and parasites (notably *Toxoplasmosis gondii*) (reviewed by Brown and Derkits, 2010). Both first and second trimester exposures have been implicated in increasing risk for schizophrenia. Accordingly, the most common models of maternal immune activation used in relation to schizophrenia are those in which pregnant rodents are systemically administered either poly(I:C) or LPS. It is generally assumed that the first two trimesters of human gestation are roughly equivalent to the entire gestation period in a rat or mouse. Thus, the time of exposure to immunogen used varies widely across rodent models, from one or two injections of immunogen early or late in gestation to once daily injections throughout the entire gestation period (reviewed by Boksa, 2010).

Outcome measures assessed in these models include a wide range of behavioral, structural, and molecular parameters deemed to be relevant to schizophrenia. The details of many of these studies were comprehensively reviewed by Boksa (2010). At a behavioral level, three of the most germane measures that have been examined are prepulse inhibition (PPI) of startle, latent inhibition, and attentional set shifting, since these can be assessed in both rodents and humans using very similar paradigms, and deficits in these have been consistently found in schizophrenia patients. PPI is the most frequently measured behavioral outcome assessed in rodent offspring from prenatal immune activation models. Consistent PPI deficits have been reported in mice administered prenatal poly(I:C), LPS, influenza virus or IL-6, and in rats administered prenatal poly(I:C) or LPS (Shi et al., 2003; Fortier et al., 2007; Smith et al., 2007; Meyer et al., 2008c; Wolff and Bilkey, 2008; Romero et al., 2010; Howland et al., 2012). Deficits in latent inhibition, a more subtle measure of attention and information processing, have also been reported in mice and

rats prenatally treated with poly(I:C) and mice prenatally treated with IL-6, however, to date, are unreported in prenatal LPS models (Zuckerman et al., 2003a; Zuckerman and Weiner, 2003; Meyer et al., 2006a; Smith et al., 2007). Recently, alterations in attentional set shifting, indicative of perseveration, have also been observed in male rat offspring prenatally administered poly(I:C) (Zhang et al., 2012). Social behavior has been shown to be impaired in maternal poly(I:C)- and influenza-treated mice (Shi et al., 2003; Smith et al., 2007), and deficits have been described in a variety of learning and memory paradigms, including spatial learning in the Morris Water Maze, for both mice and rats as a result of prenatal treatment with LPS, poly(I:C), and IL-6 (Meyer et al., 2006b; Ozawa et al., 2006; Samuelsson et al., 2006; Coyle et al., 2009).

Historically, dysfunction of the dopaminergic system has been considered a hallmark of schizophrenia neurochemistry. As such, amphetamine-induced locomotor activity and changes in brain tyrosine hydroxylase and dopamine metabolite content have been used as markers of dopaminergic activity in animal models. Extensive changes in these measures have been reported in many models of maternal inflammation; in particular, an increase in amphetamine-induced locomotion has been reported in both the offspring of mice and rats prenatally treated with poly(I:C) and of rats prenatally treated with LPS (Zuckerman et al., 2003b; Fortier et al., 2004; Meyer et al., 2008c). More recently, schizophrenia research has focused on excitatory and inhibitory amino acid transmission, with reported hypofunction of *N*-methyl-D-aspartate (NMDA) receptors and GABAergic interneurons in the frontal cortex and hippocampus in clinical and postmortem schizophrenia populations (Coyle and Tsai, 2004; Nakazawa et al., 2011). Alterations in short-term plasticity, long-term potentiation, and NMDA/ $\alpha$ -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor activity have been reported in rats prenatally treated with LPS during late gestation (Lante et al., 2008; Lowe et al., 2008; Roumier et al., 2008). Maternal administration of LPS to rats during late gestation led to reductions in hippocampal reelin and GAD67, markers of GABAergic interneurons, in the offspring (Nouel et al., 2012) while administration of poly(I:C) in early gestation in mice led to decreases in hippocampal reelin and immunogen- and sex-specific increases in GAD67 (Meyer et al., 2006b; Harvey and Boksa, 2012).

At the molecular level, there appear to be fewer parallels between described changes in brains of people with schizophrenia and the detailed molecular alterations in brains from animals subject to prenatal

immune challenge. Some studies have described long-term changes in synaptophysin, brain-derived neurotrophic factor, parvalbumin, and Akt following maternal immune activation in rodents (Golan et al., 2005; Romero et al., 2007a; Makinodan et al., 2008; Meyer et al., 2008c; Romero et al., 2010); however, these studies tend to come from single laboratories and have not yet been replicated across species or immunogen.

## Autism

Epidemiological evidence also links prenatal immune activation with an increased risk of developing autism in later life (reviewed by Patterson, 2012). For some time, this link was less established than that between schizophrenia and prenatal immune activation. Recent studies have described associations between viral infection in the first trimester, bacterial infection in the second trimester, and an increased risk for autism in the offspring (Atladdottir et al., 2010) as well as a link between elevated amniotic levels of monocyte chemotactic protein-1 (Abdallah et al., 2012), TNF- $\alpha$  and - $\beta$  (Abdallah et al., in press), and the risk of developing autism in later life. A retrospective study looking at banked sera from mothers whose offspring were later diagnosed with autism found increased levels of IFN- $\gamma$ , IL-4, and IL-5 in maternal serum at midgestation (Goines et al., 2011). Given these recent findings, much of the existing research regarding autism and prenatal immune activation has been appended onto existing animal models of prenatal infection, notably prenatal poly(I:C) and prenatal influenza administration, which have been developed with respect to schizophrenia epidemiology. This approach has proved fruitful given there are significant similarities between the disorders, with a recent article even suggesting that it may be neuroinflammatory events during early fetal development which result in this shared pathogenesis (Meyer et al., 2011).

The most well-known characteristic of autism in humans is behavioral alterations including sensory and motor deficits, elevated anxiety and impaired social interaction, communication, and emotional processing (Wing, 1997). As with schizophrenia, people with autism often have an impaired ability to filter environmental stimuli, which has been assessed using PPI (Perry et al., 2007). The PPI deficits and alterations in social interaction reported in various models of prenatal immune activation are described in the section on "Schizophrenia". Three mouse studies, one using maternal influenza administration (Shi et al., 2003) and two using maternal poly(I:C) administration (Smith et al., 2007; Malkova et al., 2012),

have described a number of behavioral changes in the offspring, including deficits in PPI, decreased social behavior, increased markers of anxiety, ultrasonic vocalization deficits, and repetitive behaviors, which mimic the behavioral outcomes of people with autism. It is interesting to note that all of these studies used a viral immunogen at early to midgestational time points to induce these behaviors; this correlates very well with recent autism epidemiology and suggests further that targeted research using these immunogens, at these time points, is warranted.

Disrupted neurochemistry and neurotransmitter function is also evident in brains of people with autism (reviewed by Lam et al., 2006). Alterations in the serotonergic system have been reported, and there is conflicting evidence on the altered function of the dopaminergic system. We have described some of the changes in dopamine system function in animal models of prenatal immune activation in the section on "Schizophrenia". Deficits in serotonin and its main metabolite have been described in various brain regions of mice prenatally treated with poly(I:C) at E9 (Winter et al., 2009), mice prenatally treated with influenza at E16 or E18 (Fatemi et al., 2008; Winter et al., 2008), and rats prenatally treated with LPS at E10.5 (Wang et al., 2009a). However, none of the studies describing these changes in serotonin included any behavioral measures of anxiety or social interaction, which could have strengthened our understanding of the potential relationship between neurochemical and behavioral changes that manifest as a result of prenatal immune activation.

Markers of hippocampal, amygdalar, and cerebellar dysfunction, including small cell size and increased cell density in these regions, a reduction in Purkinje cell number, and, developmentally, abnormally enlarged neurons in the cerebellum, are considered hallmarks of autistic brain morphology (Bauman and Kemper, 2005; Amaral et al., 2008). There have been consistent reports of alterations in cerebellar and hippocampal Purkinje cell number, size, and density in mouse models using prenatal influenza at both early and late gestational time points (Fatemi et al., 1999, 2002, 2008, 2009; Shi et al., 2009) and some isolated descriptions of cerebellar and hippocampal changes using maternal poly(I:C) in the mouse and maternal IL-6 in the rat (Samuelsson et al., 2006; Shi et al., 2009).

Finally, alterations in the central and peripheral immune system, such as changes in plasma and brain cytokines, dysregulation of immune-related genes, alterations in gastrointestinal tract permeability, and some autoimmune-like responses, have been reported in people with autism (White, 2003; Ashwood and

Van de Water, 2004). In animal models of prenatal immune activation, there are conflicting reports as to whether cytokines are induced in the fetal brain following exposure to the immunogen (Cai et al., 2000; Urakubo et al., 2001; Gayle et al., 2004; Ashdown et al., 2006; Meyer et al., 2006b). Regardless of this uncertainty, most of these markers were measured just hours following the inflammatory event. With respect to long-term effects, exposure of rats to single doses of LPS either prenatally or neonatally has been reported to result in reduced induction of plasma cytokines (IL-6, TNF- $\alpha$ , and IL-1 $\beta$ ) in response to LPS challenge in adolescence or adulthood (Hodyl et al., 2007; Galic et al., 2009b; Beloosesky et al., 2010). However, prenatal LPS or poly(I:C) treatment of rats has also been reported to result in elevated basal plasma cytokine levels later in life (Carvey et al., 2003; Romero et al., 2007a, 2010; Han et al., 2011). Currently, less is known about the long-term effect of early life infection on cytokine content in the brain, although Bilbo et al. (2005) have observed that rats injected neonatally (P4) with *E. coli* show exaggerated IL-1 responses to LPS in the hippocampus and cortex at adulthood.

### Cerebral Palsy

Important primary risk factors for cerebral palsy, including preterm birth and small birth weight, can be a result of, or induced by, maternal infection. Epidemiological evidence has also suggested that maternal infection during the first and second trimesters, intrauterine infections (such as chorioamnionitis) during the third trimester and labor, and neonatal infections (such as meningitis) are significant risk factors for cerebral palsy (Nelson and Willoughby, 2000; Reddihough and Collins, 2003; Nelson, 2008). Thus, in contrast to models for autism and schizophrenia, common animal models of prenatal immune activation for cerebral palsy involve direct intrauterine administration of LPS which often, in turn, induce preterm births (Bell and Hallenbeck, 2002). Systemic models of gestational LPS administration are also used (Cai et al., 2000; Paintlia et al., 2004).

Deep, focused and diffuse white matter injury (periventricular leukomalacia, PVL) and damage to the cortex, basal ganglia, and thalamus are the most common markers of cerebral palsy-specific brain damage (van de Bor et al., 1989; Folkerth, 2005). In a preterm model, sheep were administered intravenous injections of LPS over 5 days during late gestation. This treatment regime resulted in a brain pathology characterized by diffuse subcortical damage and PVL (Duncan et al., 2002). In a rat model, intrauterine

administration of LPS at E15 resulted in early cortical cell death and dysmyelination, similar to PVL lesions, at 3 weeks of age in the offspring (Bell and Hallenbeck, 2002). A preterm model of intrauterine LPS administration in mouse caused significant fetal brain injury (Burd et al., 2010; Ernst et al., 2010) as did a similar “to term” model (Elovitz et al., 2011).

Diffuse PVL lesions in cerebral palsy brains are initiated by loss of developing oligodendrocytes and subsequent hypomyelination, which is mediated, in part, by free radical-induced oxidative stress, glutamate toxicity, and circulating cytokines (Kinney and Back, 1998). Administration of LPS to rats during late gestation caused increases in markers of oxidative stress in the fetal brain (Paintlia et al., 2008) and in glutamate-induced hydroxyl radical release in the striatum of P14 offspring (Cambonie et al., 2004), together with an increase in circulating proinflammatory cytokines in the maternal and fetal compartments (Cai et al., 2000; Paintlia et al., 2004). Moreover, systemic LPS administration at E18 has been shown to cause loss of developing oligodendrocytes in fetal brain, as well as decreases in oligodendrocyte number and expression of myelin-related proteins in the postnatal brain (Paintlia et al., 2008). In a somewhat different model of white matter injury, using direct injection of LPS into the neonatal rat corpus callosum, decreases in preoligodendrocytes and hypomyelination have also been observed, together with increases in callosal radial diffusivity measured with *in vivo* magnetic resonance imaging (Pang et al., 2003; Lodygensky et al., 2010).

Importantly, hypoxia-ischemia is one of the causes of PVL, and a number of studies using rodent models have shown that LPS exposure exacerbates detrimental effects of hypoxia on developing brain (Eklind et al., 2005; Wang et al., 2009b). Hypoxia-ischemia is known to directly contribute to the loss of oligodendrocytes in PVL lesions (Levison et al., 2001). Thus, as hypoxia-ischemia is also a risk factor for cerebral palsy, it is likely that the combination of prenatal inflammation and a hypoxic event during gestation would result in a significant increase in oligodendrocyte loss in the fetal brain, increasing the likelihood of cerebral palsy. Preterm birth is another risk factor for cerebral palsy, and there is a strong association between *in utero* infection during pregnancy and preterm birth (Romero et al., 2007b). Prenatal administration of LPS or live bacteria in a variety of animal species are well-established models of preterm birth, and there is a rich literature describing effects of prenatal infection on fetal physiology and well-being from this perspective (Edwards and Tan, 2006; Kemp et al., 2010; Adams Waldorf et al., 2011).

Developmental Neurobiology

## Epilepsy and Acute Seizures

Postnatal rodent models have been used to investigate the role of immune activation in the generation of acute seizures and epilepsy. Acute seizures can develop as a proximate consequence of both bacterial and viral CNS infections. Mechanisms involved in the generation of such seizures have been investigated in models of bacterial meningitis involving intracisternal injection of group B streptococcus in infant rats (Kim et al., 1995; Kolarova et al., 2003) and models of viral CNS infection involving intracisternal administration of Theiler's murine encephalomyelitis virus in young mice (Libbey and Fujinami, 2011). The notion that inflammation can also enhance susceptibility to acute seizures induced by other agents or enhance CNS damage induced by seizures has been supported by studies in immature rats indicating that LPS administration enhances rapid kindling and facilitates acute seizures or seizure-induced neuronal injury induced by agents such as lithium-pilocarpine, kainic acid, or glutaric acid (Auvin et al., 2007, 2010b; Magni et al., 2011).

Several groups of investigators have provided intriguing evidence that infection or immune activation early in postnatal life can lead to long-lasting increased seizure susceptibility in adulthood. Stewart et al. (2010) showed that young mice (P28–35) receiving intracisternal injection of Theiler's murine encephalomyelitis virus developed spontaneous epileptic seizures 2–7 months after the injection. Galic et al. (2008) have demonstrated that rat pups receiving an intraperitoneal injection of LPS at a critical period in development (P7, P14) show enhanced convulsant-induced seizure susceptibility at adulthood. In a similar vein, Galic et al. (2009a) have shown that intracerebroventricular injection of poly(I:C) in P14 rat pups also causes increased seizure susceptibility at adulthood, indicating that early exposure to either bacterial or viral immunogens can contribute to this lasting susceptibility. Using a somewhat different approach, Auvin et al. have examined effects of LPS administration in combination with seizure-inducing agents such as hyperthermia or lithium-pilocarpine in immature rats; these studies showed that pairing LPS with lithium-pilocarpine resulted in more severe spontaneous seizures at adulthood compared to lithium-pilocarpine alone (Auvin et al., 2010a), while the combination of LPS and hyperthermia caused a long-term reduction in convulsant-induced seizure threshold compared with hyperthermia alone (Auvin et al., 2009).

## Parkinson's Disease

Interestingly, a subset of studies looking at prenatal administration of LPS was conducted by researchers

interested in developing a model of Parkinson's disease. A single dose of LPS at E12.5 resulted in long-lasting and progressive dopaminergic cell death and a lifelong elevation in serum TNF- $\alpha$  (Carvey et al., 2003). Subsequent articles from the same group of investigators have replicated these findings, describing a decrease in dopaminergic cells in the substantia nigra that is evident at P21 and persists until the animal is over one year old (Ling et al., 2002, 2006, 2009). These results appear to be in contrast to those described in the section on "Schizophrenia", in which prenatal treatment with LPS or poly(I:C) results in an increase in amphetamine-induced locomotion, a marker of dopaminergic activity. However, a close consideration of reported dopamine-associated changes in models of prenatal immune activation indicates that, while some researchers report an increase in dopamine cell numbers or levels of dopamine and its metabolites in various brain regions (Ozawa et al., 2006; Meyer et al., 2008a,b,c; Winter et al., 2008), others report decreases (Bakos et al., 2004; Romero et al., 2007a, 2010). As might be expected, these changes in dopaminergic parameters appear to depend on the specific model used, the stage of pregnancy at which the immunogen was administered, and on the brain region and postnatal age examined. So, although schizophrenia researchers tend to focus on alterations in amphetamine-induced locomotion as a measure of dopamine dysfunction, the relationship between behavioral markers of dopamine dysfunction and dopamine biochemistry remains to be established in these models. The example of dopamine offers a good illustration of the difficulty in synthesizing findings on prenatal and early postnatal inflammation across laboratories, given the multiplicity of models and outcome measures used by various researchers.

### General CNS Effects

There is epidemiological evidence linking fetal and early life infections with general cognitive deficits and CNS abnormalities, as well as alterations in hypothalamic-pituitary-adrenal (HPA) axis function and immune regulation (reviewed by Bale et al., 2010). Researchers have developed animal models of pre- and postnatal immune activation to explore these effects, without necessarily specifying a disease model. A wide number of immunogens are used, including LPS, as well as specific cytokines and actual disease strains, such as Borna virus.

In the absence of a specific disease context, general effects of immune activation on cognitive per-

formance in later life has been the subject of investigation in studies using, for example, rat models of prenatal or neonatal exposure to LPS or replicating *E. coli* (Bilbo et al., 2005; Harre et al., 2008; Hao et al., 2010). Since cognitive deficits are also a prominent feature of schizophrenia, effects of prenatal immune activation on cognition are also reported in studies focused on this disorder (Ozawa et al., 2006; Bitanhirwe et al., 2010; Howland et al., 2012; Zhang et al., 2012).

Animal modeling studies have also provided strong evidence that neonatal immune challenge can result in persistent modifications to the HPA axis and downstream innate immune function, resulting in altered susceptibility to inflammatory disease (e.g., arthritis) later in life (reviewed by Spencer et al., 2011). However, the implications of this neonatal immune activation are not limited to the innate immune system. For example, administration of LPS during early life can affect the adult response to cerebral ischemia in later life (Spencer et al., 2006), a measure which would, in humans, translate to a longer recovery period after stroke.

Direct administration of cytokines allows researchers to create focused models of immune activation and to observe the overall effects of specific cytokines on CNS function. In rats, daily subcutaneous administration of IL-1 $\alpha$ , IL-2, IL-6, TNF- $\alpha$ , and IFN- $\gamma$  between P2 and P10 resulted in cytokine-specific behavioral changes (Tohmi et al., 2004). At 3 weeks of age, rats treated with IL-2 displayed enhanced locomotor and exploratory activity (Tohmi et al., 2004). At 8 weeks of age, rats treated with IL-1 $\alpha$  exhibited an increase in startle response, a decrease in PPI, and an increase in social behavior. Intriguingly, rats treated with IL-6, TNF- $\alpha$ , or IFN- $\gamma$  showed no behavioral abnormalities. The prenatal intramuscular turpentine model also appears to have some degree of cytokine specificity, since only IL-6 is increased in the circulation while production of IL-1 and TNF- $\alpha$  is confined to the local site of inflammation (Luheshi et al., 1997). Administration of turpentine to pregnant rats at E15 resulted in a decrease in PPI, an increase in amphetamine-induced locomotion, prolonged fear conditioning and increased latency in a cued task in the Morris Water Maze as well as increased tyrosine hydroxylase expression in the nucleus accumbens of offspring (Aguilar-Valles et al., 2010; Aguilar-Valles and Luheshi, 2011). When turpentine was administered at E18, only the fear conditioning response was altered in the offspring (Aguilar-Valles and Luheshi, 2011). Together, these findings suggest that there are windows of vulnerability during fetal and neonatal development

during which an increase in specific cytokines may produce long lasting changes in dopamine related biology and behavior.

Models using disease strains of viruses have a two-fold advantage; while they can be used to generally model and explore the ramifications of early immune activation, they can also help us understand shared pathways between seemingly unrelated diseases. For example, neonatal infection with Borna disease virus originated as a model to examine effects of viral infection on brain development. Borna disease virus is a single-stranded, negative sense RNA virus known to cause Borna disease. With increasing insight into the neonatal Borna virus model, researchers observed that many of the downstream changes were relevant to features of autism, as well as schizophrenia (Hornig and Lipkin, 2001), although there is no epidemiological evidence to suggest that autism or schizophrenia is caused by actual exposure to Borna virus. Neonatal exposure results in animals that are stunted in growth, have altered sleep-wake cycles, decreased PPI, decreased play behavior, and altered developmental progression of motor skills (Hornig and Lipkin, 2001). As such, this model provides an intriguing alternative for researchers who are interested in studying the effects of neonatal viral infection.

### **IS EARLY LIFE INFECTION A DISEASE-SPECIFIC RISK FACTOR OR A GENERAL VULNERABILITY FACTOR? IMPLICATIONS FOR ANIMAL MODELS**

As we have seen with prenatal infection, the line of reasoning underlying an epidemiology-based approach to develop animal models of disease proceeds (roughly) as follows. Begin with a disease of interest and identify a risk factor that is associated with that disease, develop an animal model of the risk factor, and attempt to determine if the animal model mimics the disease pathology seen in humans. However, difficulties with this approach may arise because the risk factor identified for the disease of interest is also a risk factor for a number of other diseases. Therefore, when modeling that risk factor in an animal, you might expect to observe pathology related to several different diseases. As an example, both schizophrenia and autism are associated with prenatal infection as a risk factor but it is difficult to envisage how the same risk factor will lead to one of these disorders versus the other. As a corollary then, it is difficult to determine if a specific animal model of prenatal immune activation is relevant to schizophrenia or autism or both. To move forward, we may

consider two possibilities. The first is that we believe we will be able to create separate animal models of these disorders using the same risk factor, but that they will depend on identifying a specific immunogen (or class or dose of immunogen) at a specific critical time point of administration in order to lead to either schizophrenia-like or autism-like pathology. The second is that we would consider prenatal immune activation as a general vulnerability factor for both schizophrenia and autism, which requires other factors to be present, either as genetic or other environmental insults, in order to develop the disease. Differentiating between these two possibilities allows us to identify two distinct experimental plans of action.

### **Early Life Infection as a Disease-Specific Risk Factor**

A major difficulty in formulating a synthesis from the current literature on the effects of prenatal or postnatal infection on neurodevelopment arises because of the wide range of models used in separate experiments by different groups of investigators (Boksa, 2010). The models differ with respect to the immunogen used, the dose and number of administrations of immunogen, the time during gestation or postnatal life when immunogen is administered, the postnatal age and sex of offspring examined, and the type of outcome measure quantified.

Working on the idea that exposure to specific immunogens at specific time points of gestation will predispose toward different diseases, e.g., schizophrenia versus autism, fundamental information describing the effects of multiple immunogens, at multiple time points during gestation, on the same outcome measures, *within the same study*, is needed (see, for example, Meyer et al., 2006b; Fortier et al., 2007; Meyer et al., 2008c; Harvey and Boksa, 2012). These types of experiments will help to discern if there are differing effects of different immunogens or different doses of immunogens and whether critical time windows of administration are required to observe differential outcomes. These results will also help to emphasize which specific parameters of prenatal immune activation are essential to enable other investigators to replicate observed effects—as in many fields of research, independent replication of results is not a strong feature of the literature on prenatal infection and neurodevelopment. [A notable exception is the consistent deficits in PPI following prenatal poly(I:C), LPS, or influenza, which have been observed by numerous independent laboratories, see the section on “Schizophrenia”.] Conversely, it will also be important to determine if a single protocol of immunogen



administration gives rise to outcome measures specifically related to one disorder (e.g., schizophrenia) but not to others (e.g., autism). This would require that researchers interested in a particular disorder not only quantify outcome measures related to their disorder of interest but also examine a wider range of CNS outcome measures in order to examine the specificity of effects in their model. These approaches should help the field to form consensus regarding some of the most integral questions in the prenatal inflammation literature, for example, how does prenatal infection change dopamine and other neurotransmitter biochemistry, and do multiple behavioral phenotypes converge, or not, within the same model?

A further potentially fruitful avenue of investigation for researchers interested in neurodevelopmental disorders would be to consider effects of prenatal infection on systems other than the CNS that could influence their disease of interest. For example, there is human epidemiological evidence suggesting an association between exposure to measles during gestation and the onset of Crohn's disease/inflammatory bowel disease in offspring in later life (Ekblom et al., 1994, 1996; Nielsen et al., 1998; Pardi et al., 1999). Hence, it has been suggested that prenatal infection may be a risk factor for both inflammatory bowel disease and autism, and in fact, there is evidence that a subset of autistic children experience gastrointestinal abnormalities, which could be indicative of a decrease in mucosal integrity (Levy et al., 2007; de Magistris et al., 2010). Recent work has highlighted that the microbiota of the gut can play an important role in CNS function and reactivity (Neufeld and Foster, 2009). However, to date, few animal models of prenatal infection have considered the role of the gut. In the rat, neonatal exposure to LPS has been shown to result in a more severe response to induced experimental colitis (Spencer et al., 2007). No studies investigating effects of prenatal infection on neurodevelopment have included examination of the gut. Although this research is ongoing in humans, the established models of prenatal immune activation would provide an obvious and accessible model in which to test the relationship between gut microbiota and behaviors relevant to autism. One could envisage how investigations of this sort might conceivably lead to a description of specific situations in which prenatal infection could lead to autism, as opposed to other CNS disorders.

### **Early Life Infection as a General Vulnerability Factor**

If we consider that prenatal infection is a general vulnerability factor conferring increased susceptibility to

a range of different neurodevelopmental disorders, then it is more important than ever to create multifactorial models, combining either multiple environmental risk factors or an environmental risk factor on a background of genetic risk. This approach has been used by groups examining the interactive effects of prenatal immune activation together with exposure to environmental neurotoxins (Ling et al., 2004a,b, 2006) or effects of prenatal immune activation in interaction with genes implicated in the etiology of disorders such as schizophrenia and Parkinson's disease (Granholm et al., 2010; Ibi et al., 2010; Ehninger et al., 2012; Vuillermot et al., 2012). In theory, such investigations may allow us to identify which combinations of etiological factors are more likely to result in one particular disorder (e.g., schizophrenia) versus another (e.g., autism). Of course, this type of multifactorial animal model adds another layer of complexity onto an already complicated prenatal infection model and presents further challenges in attempts to summarize how prenatal infection affects neurodevelopment using a synthesis of findings from various laboratories.

### **CONCLUDING REMARKS**

Prenatal and early postnatal infections have been associated with increased risk for a number of neurodevelopmental disorders. Animal models of prenatal and early postnatal immune activation have contributed substantially toward indicating that this association may be causal. However, for the most part, animal models have not yet shed light on the question of which specific conditions are required in order for early life infection to contribute to development of one particular disorder as opposed to another (e.g., schizophrenia or autism?). We have discussed the dichotomy that exists between the belief that a specific CNS disorder resulting from early life infection may be determined by exposure to a particular class of pathogen at a critical time point in fetal or postnatal development, and the theory that the combination of early life infection with specific additional genetic and environmental insults will determine the neurodevelopmental outcome. In fact, these two ideas need not be thought of as mutually exclusive. One can readily envisage the scenario where the actual etiology of a complex neurodevelopmental disorder like schizophrenia or autism might require both exposures to a specific infection at a specific time in early development in combination with further environmental and genetic "hits." A consideration of these two approaches will be useful when designing robust and

reproducible animal studies that can be integrated into our current knowledge and contribute to the progression of the prenatal and postnatal immune activation literature.

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