The Timing and Specificity of Prenatal Immune Risk Factors for Autism Modeled in the Mouse and Relevance to Schizophrenia

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Key Words

Autism • Mouse model • Prenatal infection • Inflammation • Schizophrenia • Infection • Pregnancy

Abstract

Autism is a highly heritable condition, but there is strong epidemiological evidence that environmental factors, especially prenatal exposure to immune challenge, contribute to it. This evidence is largely indirect, and experimental testing is necessary to directly examine causal mechanisms. Mouse models reveal that prenatal immune perturbation disrupts postnatal brain maturation with alterations in gene and protein expression, neurotransmitter function, brain structure and behavioral indices reminiscent of, but not specific to, autism. This likely reflects a neurodevelopmental spectrum in which autism and schizophrenia share numerous genetic and environmental risk factors for difficulties in social interaction, communication, emotion processing and executive function. Recent epidemiological studies find that early rather than late pregnancy infection confers the greater risk of schizophrenia. The autism literature is more limited, but exposures in the 2nd half of pregnancy may be important. Mouse models of prenatal immune challenge help dissect these observations and show some common consequences of early and late gestational exposures, as well as distinct

ramifications potentially relevant to schizophrenia and autism. Although nonspecificity of immune-stimulated mouse models could be considered a disadvantage, we propose a broadened perspective, exploiting the possibility that advances made investigating a target condition can contribute towards the understanding of related conditions.

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Introduction

Autism is a highly genetic neurodevelopmental disorder [1–7], characterized by a triad of repetitive and stereotypic behaviors, impaired communication and marked difficulties in social reciprocity [8, 9]. Postmortem studies date the onset of neuropathology as early as fetal life [10, 11] and there is increasing evidence that this results in postnatal anatomical abnormalities in fronto-temporo-parietal cortices, the limbic system and cerebellum [12–18], and white matter abnormalities [14, 19], which may contribute to functional asynchrony in BOLD (blood oxygenation level-dependent) signals reported during higher-order cognitive processing autism [20–24].

The etiology of autism spectrum disorders remains mysterious. Although autism is a highly heritable condition, genetics alone cannot fully account for the condi-

tion. There is strong evidence that environmental factors, especially prenatal life exposures, also contribute to autism [25–29]. Disentangling the effects of environment and genes in clinical populations is challenging. Increasingly, the need for direct experimental testing of causal mechanisms is appreciated. This can be achieved through mouse models, with the caveat that no mouse model can capture the uniquely human aspects of autism. However, the mouse system readily gives access to basic mechanisms underlying complex behaviors. Rodent biology is remarkably similar to man and, with a lifespan of around 2 years, developmental and maturational processes can be compressed *in vivo*. This facilitates the rapid translation of successful basic science research in the laboratory to clinical application.

Even though superficially quite distinct, autism spectrum conditions have a number of points of overlap with other neurodevelopmental conditions, such as schizophrenia. People with autism spectrum have a strong family history of schizophrenia and bipolar disorder [30], and have alterations in the same set of genes [31, 32]. Neuroanatomically, both conditions lead to abnormalities in frontostriatal systems [13, 14, 27–29, 33–38] and individuals with autism spectrum may even suffer from psychosis [39]. Asperger's syndrome is associated with higher scores on measures of paranoia than is typical [40]; 'negative' symptoms reminiscent of schizophrenia in people with Asperger's syndrome partly respond to the antipsychotic risperidone [41], and antipsychotics can improve some symptoms of autism [42, 43].

Social interaction, communication, emotion processing and executive function abilities are disrupted by both conditions; both involve unusual responsiveness to the environment and impaired stimulus filtering (measured by a failure of sensorimotor gating in the prepulse inhibition of startle paradigm) [17, 44–46]. Indeed, autism was originally referred to as a 'schizophrenic syndrome of childhood' or 'childhood psychosis', and has been suggested to lie on the same spectrum as schizophrenia [34, 47]. One way to conceptualize this is to consider that it is not the autistic or schizophrenic condition itself which is inherited, but rather altered neurodevelopment [48]. However, others take an alternative position and argue that schizophrenia and autism are 'diametrically opposite' [49].

Therefore the study of the neurobiology of behaviors relevant to autism using the mouse is necessarily limited by specificity, making it unlikely that mouse models generated will apply only to autism. As a result, the choice of behavioral paradigms which examine face validity of

mouse models becomes problematic. Most test procedures which can be interpreted as relevant to autism, are also relevant to schizophrenia. For example, impaired sensorimotor gating, measured in prepulse inhibition of startle (PPI) procedures, has been reliably documented in schizophrenia [45, 46]. Initial study of sensorimotor gating in a broad spectrum of participants with autism returned inconclusive findings [50]. However, in a more homogeneous sample of adult men with Asperger's syndrome, we observed sensorimotor gating anomalies [17], and others have replicated this finding in individuals with high functioning autism [44].

A number of conditions involving frontostriatal system pathology are known to disrupt PPI, including obsessive compulsive disorder [51]. Nevertheless, this paradigm has come to be included as a core component of any battery testing autistic-like phenotype in mouse models. The advantage is that PPI is readily observed in all mammals under similar stimulus parameters. Such cross-species utility makes PPI among the most useful of translational tasks for animal models of neurodevelopmental disorders [52–55]. Additional behavioral phenotype measures which have face validity for autism spectrum may also apply more generally to neurodevelopmental disorders. A battery of behavioral tasks relevant to autism has been comprehensively documented [56, 57]. These include probes for various social behaviors and response perseveration, which although altered in autism [58] are also affected by other conditions, including schizophrenia [59, 60]. This lack of specificity can be seen as a disadvantage, but perhaps more realistically it demands a broadened perspective, open to the possibility that advances made investigating a target condition can contribute towards understanding related conditions.

Prenatal Immune Activation Alters Postnatal Neurodevelopment

Maternal infection during prenatal life is implicated in the etiology of both autism and schizophrenia [29, 61–67] and maternal viral infection has been suggested to be 'the principal nongenetic cause of autism' [68]. That maternal infection can precipitate neurodevelopmental sequelae relevant to autism or schizophrenia has been directly tested using rodent models of maternal immune activation (MIA) with respiratory infection, borna virus and influenza [69–75].

Influenza

The Fatemi group has contributed a rich body of work examining the consequences of prenatal infection with influenza virus using the mouse. Prenatal influenza infection has been reported to impair PPI in the offspring, and cause deficits in open field, novel object exploration and social interaction [76]. Influenza infection of pregnant mice also interrupts migration and causes loss of cerebellar Purkinje cells in the offspring [77], a hallmark of autism [78] which is also observed in schizophrenia [79]. Prenatal exposure has a considerable and widespread impact on the expression of key regulatory proteins in brain. It has been shown to decrease the expression of reelin in the postnatal hippocampus [80]. Reelin is a neuroregulatory protein of critical importance during the development of the central nervous system [71] and its expression is disrupted in autism [81–84] and other neurodevelopmental conditions, including schizophrenia and bipolar disorder [79, 81, 85]. Changes in expression of a number of genes coding for structural and functional proteins are triggered by prenatal influenza exposure. Exposure to influenza on gestation day (GD) 9 modifies expression of chaperones, HSC70, bicaudal D, aquaporin 4, carbonic anhydrase 3, glycine receptor, nor-epinephrine transporter and myelin basic protein [86]. Later exposure to influenza on GD16 also alters myelin basic protein, expression of other myelination genes (e.g. Mbp, Mag, and Plp1) and fractional anisotropy (FA) measures, a diffusion tensor MRI marker of white matter integrity [87]. The importance of timing of prenatal exposure to postnatal outcomes is discussed further below.

Polyinosinic:Polycytidylic Acid

A complementary collection of experiments has been designed to show that many consequences of MIA are not pathogen-specific. For example the viral analogue polyinosinic:polycytidylic acid (PolyI:C) administered during pregnancy is sufficient to drive the MIA phenotype which encompasses a wide spectrum of behaviors including conditioning anomalies, impaired PPI and hypersensitivity to amphetamine challenge [88–98]. The brain structural basis of these behavioral abnormalities may involve white matter systems. Early prenatal exposure to PolyI:C, at the time when oligodendrocytes are generated in the ganglionic eminence (GD9.5), delays myelination processes during postnatal brain maturation [99]. In our own studies, we found prenatal PolyI:C leads to wide-

spread bidirectional changes in FA which were associated with concomitant alterations in the level of an immunohistochemical marker for oligodendrocytes (CNPase) [100].

Interleukin-6

In an elegant series of experiments, Smith et al. [101] isolated the cytokine interleukin-6 (IL-6) as a key mediator of the effects of PolyI:C. A single injection of IL-6 administered to pregnant mice on day 12.5 was sufficient to precipitate adult PPI and latent inhibition deficits usually consequent on PolyI:C exposure. Simultaneous injection of an anti-IL-6 antibody prevented a wide range of behavioral deficits and gene expression changes caused by prenatal PolyI:C. Most convincingly, IL-6 knockout mice were resistant to the effects of MIA [101]. However, elevation of other cytokines, such as IL-2, in early life have also been shown to elicit behavioral changes, such as increased activity in open field and impaired acquisition of a conditioned eye-blink response [102].

IL-6 is now appreciated to have widespread effects on early neuronal differentiation. IL-6 has been shown to support survival of basal forebrain cholinergic cells in culture and promote differentiation of tyrosine hydroxylase-positive catecholamine cells [103, 104]. This is a striking observation because very recent investigation [105] has shown that, on GD18, choline acetyltransferase, a marker of cholinergic neurons, is increased in the basal forebrain of mice previously exposed to PolyI:C on day 12.5. IL-6 plays a major part in this effect as the same result is not seen in IL-6 knockout mice. In addition, PolyI:C administered on GD9 has been shown to increase the numbers of tyrosine hydroxylase-positive neurons in the dopamine-rich substantia nigra of the fetal mouse [106]. Furthermore, the projection pathways from these neuronal populations coincide with regions of increased fractional anisotropy (a measure of white matter microstructural integrity) in adult mice exposed to PolyI:C prenatally [100], suggesting that MIA via IL-6 has far-reaching effects on the development of major neurotransmitter circuits in the mouse brain.

Microglia produce IL-6 and their activation in the fetal brain has been suggested to contribute to the action of maternal inflammation on brain development in the MIA model [105]. Microglia migrate to the mouse fetal brain in mid-gestation and at this time are found in the ganglionic eminence (containing the progenitor cells of caudate, putamen, amygdala) [107] and around the Cajal-

Retzius cells, the reelin-producing cells which guide cortical organization. It is compelling that a rich density of IL-6R can be stained along the ganglionic eminence, where IL-6-producing microglial cells are in such abundance. The ganglionic eminence persists until term [108], making it potentially a target of IL-6-mediated effects on neuronal migration and differentiation throughout gestation. Evidence that the germinal matrix is especially vulnerable to inflammatory mediators comes from observations of subependymal cysts at the head of the caudate following congenital rubella infection [109]. Indeed, prenatal rubella infection is associated with autism, and subependymal cysts have been reported in children with autism who had congenital infection [67].

Lipopolysaccharide

Driving immune activation through the bacterial mimic, lipopolysaccharide triggers a postnatal phenotype change similar to that induced by viral-type response, including PPI deficits [110] and hypersensitivity to amphetamine challenge [111] in rats. Behavioral disruption in mice offspring exposed to maternal lipopolysaccharide on GD17 has also been reported [112]. Lipopolysaccharide administered to pregnant mice on day 15 of gestation caused elevated IL-6 in maternal sera and in amniotic fluid [113], implying that bacterial and viral challenges may trigger similar changes in cytokine response in the pregnant mouse. Resisting this position are findings that both the timing of MIA and the viral or bacterial-like nature of the challenge have distinct repercussions on the phenotype, at least in the rat [111]. This will be discussed further below, but in general terms, the bulk of experimental work on rodents supplements clinical evidence of a role for the immune system in modifying the neurodevelopmental trajectory of vulnerable individuals [114–117].

Maternal Anti-Fetal Brain Antibody

Another piece of the puzzle surrounding early life immune mechanisms in autism has recently come to light. Some mothers of children with autism secrete antibodies for prenatally expressed brain antigens. These have been proposed to cross the placenta and modify brain development in the fetus, with persistent postnatal effects [118, 119]. Modeling this effect, serum from mothers with autistic children has been administered to pregnant mice.

Offspring born to mice exposed to the human sera showed increased activity in open field, greater anxiety and greater acoustic startle response in addition to altered sociability. This behavioral phenotype was accompanied by glial activation [120, 121], which has been reported in post-mortem studies of both autism [117] and schizophrenia [122].

One criticism of this and other mouse models developed to understand autism is the nonspecific nature of the behavioral changes described, and whether these truly map to the human condition. Certainly, the mouse can never replicate uniquely human attributes, but much behavior does have cross-species analogy. To a large degree the problem of nonspecificity is compounded by the fact that autism is a constellation of features, none of which is itself specific to the autistic spectrum. To address this, the pregnancy antibody challenge has also been given to non-human primates, and offspring born to rhesus monkeys exposed to sera from mothers of children with autism showed increased repetitive and stereotypic behaviors [118]. In that study, the serum administered was collected from the mothers of more than 1 child with autism. There is potential for pregnant mothers to become sensitized to fetal blood cells during gestation [123], but the likelihood that a mother produces antibodies against fetal leukocyte antigens increases with parity [124]. IL-6, produced by T helper 2 cell populations, promotes B cell maturation and antibody production. Moreover, progesterone at the fetal-maternal interface promotes TH2 responses, as does estrogen [121]. Thereby mechanisms which elevate IL-6 may also cause increased antibody production.

Postnatal Phenotype Depends upon the Timing of Prenatal Exposure

While MIA cannot be said to be specific to autism or schizophrenia, it is clear that the precise timing of MIA does affect the phenotypic outcome on a number of dimensions. From an epidemiological perspective, the data obtained by previous retrospective research implicated mid-pregnancy as a window of vulnerability for infection-induced schizophrenia risk [125–128]. This early work has been superseded by studies using serological markers to indicate maternal infection in the early stages of pregnancy (i.e. in the 1st trimester of human pregnancy) carries the greatest risk [62]. The possible influence of timing of infection on risk of autism has not been examined quite so comprehensively, but there are clues. Post-mortem histopathological investigation points to a failure in neuronal maturation before 30–32 weeks gestation [10, 129, 130]. This is consistent with reports of a higher

Table 1. Postnatal effects of immune stimulation at different time points during mouse gestation

	Schiz	Pol	Flu	IL-6*	POL	IgG	Flu	LPS	POL	ASD	References
Gestation day in mouse	9	9	12	12 or 13	13 to 18	16 or 18	17	17	17		
<i>Phenotype</i>											
PPI	↓	↓	↓	↓	↓				↔	↔/↓	17, 46, 50, 76, 88, 95, 101
Open field	↑	↓	↓	↓		↑			↔	↓	76, 93, 101, 120, 150
Novel object exploration	↔							↑		↓	112, 150, 151
Social interaction	↓		↓	↓		↓				↓	8, 76, 101, 120, 152
Spatial working memory	↓	↔/↓						↔	↓	↓	91, 95, 153, 154
Perseveration (resistance to rule reversal)	↑	↔							↑	↑	58, 59, 93
Latent inhibition	↓	↓		↓					↔/↑		90, 91, 101, 155, 156
Passive avoidance	↓							↓			112, 157
Antipsychotic response	↑		↑							↑	37, 43, 76, 158
Psychomimetic response/dopaminergic activity	↑	↑	↑				↔/↑		↑	↑	76, 91, 95, 138, 139, 149
Purkinje cells	↓		↓		↓			↔		↓	77–79, 113
Reelin	↓	↓	↓						↓	↓	79–82, 85, 95
Myelination processes/gene/protein expression	↓	↓	↓			↓	↓			↓	86, 87, 99, 100, 159–161
Glial activation	↑				↑	↑				↑	105, 117, 120, 121
Fractional anisotropy	↓	↑	↑			↓	↓		↓	↑	19, 35, 87, 100
Lateral ventricles	↑	↑	↓			↔	↔	↔	↓	↓	36, 71, 88, 112, 120, 141, 148

* Direct effect of IL-6 or inferred from neutralization or knockout models. ↑ = Enhanced or improved; ↓ = reduced; ↑↓ = bidirectional findings; ↔ = unchanged; blank = undetermined; Schiz = schizophrenia; ASD = autism spectrum; POL = PolyI:C; Flu = influenza; LPS = lipopolysaccharide; IgG = sera from human mothers of autistic children. This table is not exhaustive, please see text for further details.

incidence of prenatal stressors during 21–32 weeks gestation in autism [131] and a greater increase in risk of autism following exposure to very severe stress in later rather than early pregnancy [132]. Complementing studies pointing to a 2nd trimester or later window for autism is data showing that mothers diagnosed with asthma or allergies in 2nd trimester have an increased risk of having a child with autism. Of note, Zimmerman et al. [119] have described antibody response in mothers with autistic children as directed against fetal (GD18, equivalent to human 2nd trimester), but not early postnatal (day 8), rat brain protein. Still, the story is likely to be complicated, and a recent investigation of maternal infection requiring hospitalization during pregnancy found risk of autism in children born to these mothers was increased by viral infection in the 1st trimester, and by bacterial infection in the 2nd trimester [133]. However, evidence from clinical studies can be difficult to interpret and as the authors of the latter study acknowledge, their data excluded the likely large number of infections not requiring hospitalization. They suggested the work be considered exploratory and numerous possible confounding

factors, such as the severity of the infection, general immune status of the mother, comorbid conditions, comorbid infections and drug treatment, could have influenced the results.

In experimental mouse models, exposure to early and late gestational windows has been examined (see table 1 for summary of the main findings). GD9 and GD17 in the mouse approximate to the end of the middle of the 1st and 2nd trimester of human pregnancy respectively [134, 135]. In studies using PolyI:C, early maternal immune activation on GD9 impairs prepulse inhibition and causes hypersensitivity to amphetamine challenge in the adult offspring [90, 91]. While this behavioral profile does translate well to schizophrenia [45, 46, 136, 137], deficits in PPI are found in the autism spectrum [17, 44] and autism is also complicated by an overactive dopamine system [138, 139]. In contrast, GD17 exposed offspring have minimal PPI deficits [88] and are resistant to acquiring a rule reversal [93]. This phenotype is pertinent to autism, given that PPI deficits are not always observed [50] and a significant resistance to change is a feature of many in the spectrum. That said, strong resistance to change, or ‘in-

sistence in sameness', may characterize a discrete subgroup of individuals within the autism spectrum, independent of language, gender, age, IQ and other symptom domains [140]. Thus, the heterogenic effects of different time points of exposure may mirror the heterogenic nature of the autism spectrum.

Meyer et al. [93] have carefully dissected the fetal brain response to maternal immune challenge at early and late pregnancy time-points. At 3 h after treatment, maternal immune stimulation on GD9 led to a large increase in IL-6 and decrease in IL-10 in the fetal brain. In contrast, GD17 exposure decreased IL-6 and increased IL-10 in the fetal brain at 3 h after treatment. However, at 6 h after treatment, IL-6 was elevated in the fetal brain regardless of the time-point of exposure. In the same study, Meyer's team showed that reelin expression in the hippocampus of 24-day-old offspring was decreased more following GD9 exposure to PolyI:C than later exposure. Thus, the consequences of PolyI:C exposure on reelin on GD9 appear to coincide with influenza administered on the same time-point, although unlike the immediate response to PolyI:C, the immune response to influenza infection would be expected to peak a few days after the acute event [76].

The consequences of prenatal exposure to human influenza virus have also been examined at 2 different time-points in mice. Exposure on GD18 alters the expression of genes associated with both schizophrenia and autism such as *Sema3a*, *Trfr2* and *Vldlr* [141]. Influenza exposure on GD9 perturbs reelin and GFAP protein levels in the offspring [80, 142]. Either GD9 or GD18 exposure to influenza virus causes upregulation of the transcription factor *Foxp2* [141, 143], previously associated with schizophrenia [144] and autism [145]. Thus, there is some degree of overlap in both fetal brain immune response and subsequent gene expression following influenza MIA. However, there are also quite distinct responses to the same challenge at different time-points which may respectively contribute to the common and divergent postnatal behavioral phenotypes reported.

Complicating this story is imaging data showing that mice exposed to a maternal immune challenge early, but not later, in prenatal life develop ventriculomegaly [88]. Increased lateral ventricular volumes is the most consistently reported finding in schizophrenia brain imaging literature [146, 147], but is not associated with autism. In contrast, smaller lateral ventricular size has been reported in autism [148], and mice exposed to PolyI:C in late pregnancy have decreased CSF volumes in the lateral ventricles [88]. The data from experimental influenza exposure is partly conflicting. By adulthood, mice exposed

to influenza virus on GD9 have decreased lateral ventricle volume and macrocephaly, as reported in autism [71]. A later exposure to influenza on GD18 caused brain atrophy and no change in ventricular volume [141]. One possible reason for this divergence in results following PolyI:C or influenza exposure may reside in the timing of cytokine elevation. PolyI:C triggers an acute, but short-lived rise in cytokine production within a few hours of injection. Influenza aerosol contamination takes a few days to generate a peak response; therefore, influenza exposure on GD9 is perhaps better compared to the effects of PolyI:C administration on GD12 [76]. Clearly, some effects of viral-like immune challenge in early or late pregnancy are dissociable and the impact of timing of prenatal immune challenge is not a simple matter of severity [97]. In terms of ventricular indices of global brain maturational differences, early or later immune activation may shift development along a path which is more 'schizophrenia-like' or more 'autism-like', respectively. However, the shared aspects of the early and late phenotype described in mouse models mirror well the many shared features of neurodevelopmental conditions such as autism and schizophrenia [31, 34, 47, 48].

The possible divergence of phenotype to either end of an autism-schizophrenia spectrum depending on the time-point of MIA is supported by evidence from studies looking at the time course of onset of postnatal abnormalities following early prenatal immune activation. Schizophrenia is characterized by a 'latent' phase of the disease in childhood, followed by prodromal symptoms in adolescence and postponement of full clinical presentation, usually until early adulthood. There is accumulating evidence that earlier exposure to PolyI:C indeed precipitates the fullest behavioral change only in adult offspring. Meyer et al. [94] have shown that GD9 exposure to PolyI:C leads to enhanced sensitivity to an amphetamine, but not MK801 challenge in open field in adolescence. By adulthood, MK801 triggered an enhanced response. Moreover, only in adulthood are immunoreactivity measures of tyrosine hydroxylase increased and D1R, and GluR1R immunoreactivity decreased in prenatal exposed mice [94, 95]. In a subsequent longitudinal study, the latter group reported MIA induced age-dependent alterations in the number of midbrain dopamine cells and presynaptic dopaminergic markers in striatum [106]. This collection of studies, mapping dynamic changes in development and maturation of the neurotransmitter systems, including the dopamine system, may hold particular relevance to schizophrenia since the greatest changes appear in adulthood. There have been fewer lon-

gitudinal studies of offspring of mice exposed in late pregnancy. Following influenza infection on GD18, relative to sham controls, offspring had increased cerebellar dopamine levels at birth and decreased serotonin levels on postnatal day 14, but no differences in either transmitter by adulthood [149]. Clearly the consequences of prenatal immune challenge have complex effects on the precise phenotype of the offspring and on the postnatal time course of pathology.

Conclusions

Mouse model work provides direct experimental evidence that prenatal immune perturbation alters the postnatal developmental trajectory. The alterations in gene

and protein expression, neurotransmitter function, brain structure and behavioral indices are strongly reminiscent of autism spectrum. However, the effects of prenatal immune activation are unlikely to be specific to the autism spectrum, and hold relevance to other neurodevelopmental conditions, particularly schizophrenia. This most likely reflects the complex nature of a neurodevelopmental spectrum which includes autism and schizophrenia [31, 34, 48]. Although important information has already been gleaned by modeling the mechanisms set in process by prenatal inflammatory risk factors in the mouse, much remains to be extracted from this line of enquiry. It is clear that these and other mouse models of autism hold considerable potential to guide prevention strategies and encourage design of novel interventions.

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