Prenatal Poly(I:C) Exposure and Other Developmental Immune Activation Models in Rodent Systems

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It is increasingly appreciated that altered neuroimmune mechanisms might play a role in the development of schizophrenia and related psychotic illnesses. On the basis of human epidemiological findings, a number of translational rodent models have been established to explore the consequences of prenatal immune activation on brain and behavioral development. The currently existing models are based on maternal gestational exposure to human influenza virus, the viral mimic polyriboinosinic-polyribocytidilic acid [Poly(I:C)], the bacterial endotoxin lipopolysaccharide, the locally acting inflammatory agent turpentine, or selected inflammatory cytokines. These models are pivotal for establishing causal relationships and for identifying cellular and molecular mechanisms that affect normal brain development in the event of early-life immune exposures. An important aspect of developmental immune activation models is that they allow a multifaceted, longitudinal monitoring of the disease process as it unfolds during the course of neurodevelopment from prenatal to adult stages of life. An important recent refinement of these models is the incorporation of multiple etiologically relevant risk factors by combining prenatal immune challenges with specific genetic manipulations or additional environmental adversities. Converging findings from such recent experimental attempts suggest that prenatal infection can act as a "neurodevelopmental disease primer" that is likely relevant for a number of chronic mental illnesses. Hence, the adverse effects induced by prenatal infection might reflect an early entry into the neuropsychiatric route, but the specificity of subsequent disease or symptoms is likely to be strongly influenced by the genetic and environmental context in which the prenatal infectious process occurs.

Key Words: Animal model, autism, cytokines, infection, maternal immune activation, schizophrenia

The idea that altered neuroimmune mechanisms might play a role in the development of schizophrenia and related psychotic illnesses attained increasing popularity in recent years. A first line of evidence supporting such mechanisms might even date back more than 100 years. Karl A. Menninger was one of the first to reveal an association between influenza exposure and subsequent psychotic disease in patients who were admitted to the Boston Psychopathic Hospital subsequent to the outbreak of the 1918 influenza pandemic (1). In his early observational study, Menninger documented the clinical courses of 80 patients admitted to the psychiatric hospital with "mental disturbances" associated with influenza, of whom 16 were diagnosed with delirium, 25 with dementia praecox, 23 with "other types of psychosis," and 16 who were left unclassified (1). After it had largely sunken into oblivion, this early neuroimmune hypothesis of psychotic disease was reanimated by the seminal work of Torrey *et al.* (2) in the 1970s suggesting that latent viruses might be involved in the development of schizophrenia. The field has since greatly expanded, and various infectious agents are now being considered to play an etiopathological role in schizophrenia and related disorders (3).

Within this neuroimmune framework of psychotic disease, a great deal of interest has been centered upon the possible contributions of infections in prenatal life. The prenatal period seems highly sensitive to the damaging effects induced by environmental insults such as infections (4). Indeed, infection-induced disturbances directed at the maternal host can lead to pathophysiological changes in the fetal environment and negatively affect the normal course of early brain development of the offspring. This can have long-lasting consequences for the emergence of postnatal brain dysfunctions, in which relevant cerebral insults or pathological processes occur during early brain development (4). Such processes seem particularly relevant for schizophrenia and other disorders with developmental etiologies, including autism and bipolar disorder, which are all believed to be associated with aberrations in early neurodevelopmental processes (5,6).

The prenatal infection hypothesis of schizophrenia received a strong boost in the 1980s after Mednick *et al.* (7) reported an increased risk of schizophrenia after prenatal maternal exposure to an influenza epidemic in greater Helsinki. Prenatal exposure to a number of other viral agents have since been associated with schizophrenia risk, including rubella (8), measles (9), polio (10), herpes simplex (11), as well as bacterial pathogens causing sinusitis, tonsillitis and pneumonia (12), genital and/or reproductive infections (13), and the protozoan parasite *Toxoplasma gondii* (14). Importantly, prospective epidemiological research has provided serologic evidence for at least some of the pathogens implicated in the prenatal infectious etiology of schizophrenia (15). For example, two epidemiological studies using prospectively collected and quantifiable measurements have provided serologic evidence that maternal influenza infection during pregnancy increases the risk of schizophrenia of the offspring (16,17). Epidemiological studies involving clinical examination and serological testing have also confirmed a higher risk of schizophrenia and other psychosis-related disorders after prenatal exposure to rubella virus (8) and *Toxoplasma gondii* (14,18), whereas they have thus far provided equivocal results with respect to the role of herpes simplex virus (19,20) and specific cytokines (21,22).

The prospective nature of such epidemiological studies, in which a specific infectious pathogen or inflammatory marker in

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prenatal life is accessible to quantitative measurements, is arguably a very powerful approach to link developmental immune abnormalities with the neuropsychiatric disease risk. For ethical and technical reasons, however, human epidemiological research cannot directly establish causality for such associations and is often limited in its capacity to unravel the downstream cellular and molecular mechanisms affecting normal brain development. Experimental research in animals provides a unique opportunity to overcome these limitations, and this is perhaps the best reason "why schizophrenia epidemiology needs neurobiology," as pointed out by McGrath and Richards (23). An increasing number of experimental studies in rodents (24,25) and more recently in monkeys (26) now provide robust evidence for the emergence of long-term functional and structural brain abnormalities after prenatal exposure to specific infectious or inflammatory agents. This review provides a concise overview of existing developmental immune activation models in rodent systems and discusses their value to the identification of developmental neuroimmune factors relevant to schizophrenia and beyond.

The Beginning: Models of Viral Infections

Fatemi *et al.* (27) have pioneered, on the basis of the reported association between prenatal influenza infection and adult schizophrenia (7,16,17), an experimental mouse model of prenatal exposure to human influenza virus in mice. In this model, pregnant mice on gestation day 9 receive intranasal infusion with a sublethal dose of a mouse-adapted human influenza strain, and the long-term brain and behavioral effects are then evaluated in the resulting offspring relative to control offspring born to mock-infected mothers. By exposing pregnant dams to influenza virus at distinct gestational stages, the prenatal influenza model has also been used to explore the impact of the precise prenatal timing (27). As extensively reviewed elsewhere (24,25,27), maternal influenza infection in mice leads to a variety of neuropathological signs in the brains of the offspring postnatally, some of which are dependent on the precise timing of influenza exposure. These neuropathological signs include deficient corticogenesis and brain atrophy, impaired development of the corpus callosum, reduced hippocampal volumes, and decreased expression of γ-aminobutyric acid (GABA) markers such as Reelin (27–30). Furthermore, long-term deficiency in serotonin (but not dopamine) production is present after prenatal exposure to influenza virus in mice (31). Prenatal exposure to influenza virus in mice also induces a set of behavioral abnormalities in adulthood (32,33), some of which are highly relevant to schizophrenia and related psychotic illnesses (Table 1). At least some of the prenatal influenza-induced behavioral deficits can be normalized by acute administration of typical or atypical antipsychotic drugs (30,33), suggesting that they are sensitive to treatments used in the symptomatic pharmacotherapy of psychotic illnesses.

The mouse prenatal influenza model has recently extended to experimental investigations in rhesus monkeys, demonstrating the emergence of reduced gray and white matter in distinct cortical and parieto-cortical brain regions of neonates born to influenza-infected mothers (26). The extension of such translational research to rhesus monkeys is especially relevant in the present context, because prenatal corticogenesis is more advanced in primate as compared with rodent species, and therefore, primate models help to verify the relevance of findings in animal models to the human condition. Taken together, the experimental data obtained in mouse and primate prenatal viral infection models can be taken as experimental evidence to support causal effects of prenatal influenza infection in the development of long-term brain abnormalities.

Significant changes in postnatal brain structure and function have also been observed in rats and mice born to mothers exposed to other viral, bacterial, or parasitic infections (Supplement 1).

The Present, Part 1: Models of Viral-Like Immune Activation by Polyriboinosinic-Polyribocytidilic Acid

Another class of animal models of prenatal immune challenge makes use of immune-activating agents that evoke cytokine-associated immune responses in the mother without using live viral or bacterial pathogens (24,25). These models were initially developed to test whether altered expression of maternal and/or fetal cytokines might assume a key role in mediating the link between maternal infection during pregnancy and abnormal brain development in the offspring (34,35). One of the most popular and widely used methods nowadays is maternal administration of polyriboinosinic-polyribocytidilic acid (poly[I:C]) (32). Since its initial application in mouse developmental biology, the prenatal poly(I:C) model has exerted an appreciable impact on researchers concentrating on the neurodevelopmental and neuroimmunological basis of complex human brain disorders such as schizophrenia (32).

In the mouse prenatal poly(I:C) model, pregnant dams are exposed to the immunological manipulation at a specific gestational stage, and the brain and behavioral consequences of the prenatal immunological manipulation are then compared in the resulting offspring relative to offspring born to vehicle-treated control mothers (32). Poly(I:C) is a commercially available synthetic analog of double-stranded RNA. Double-stranded RNA is generated during viral infection as a replication intermediate for single-stranded RNA or as a by-product of symmetrical transcription in DNA viruses (36). It is recognized as foreign by the mammalian immune system primarily through the transmembrane protein toll-like receptor 3 (36). Transmembrane protein toll-like receptors are a class of pathogen recognition receptors that recognize invariant structures present on virulent pathogens. Upon binding to toll-like receptor 3, double-stranded RNA or its synthetic analog poly(I:C) leads to the expression of an extensive collection of innate immune response genes and proteins. The array of these responses involves the production and release of many pro-inflammatory cytokines, including interleukin (IL)-1β, IL-6, and tumor necrosis factor (TNF)-α (37). In addition, poly(I:C) is a potent inducer of the type I interferons (IFNs): IFN-α and IFN-β (38). Administration of poly(I:C) can therefore efficiently mimic the acute phase response to viral infection (38) and leads to significant inflammatory processes in the fetal brain when given systemically to pregnant dams (39,40).

As extensively reviewed elsewhere (24,25,32), numerous neurochemical and brain morphological abnormalities have been detected in adult mice and rats after maternal gestational exposure to poly(I:C). An increasing amount of rodent studies further provides robust evidence for the emergence of a multitude of behavioral, cognitive, and pharmacological dysfunctions after prenatal poly(I:C)-induced immune activation (Table 1). One intriguing feature of the prenatal poly(I:C) model is that the full spectrum of behavioral, cognitive, and pharmacological abnormalities only emerges after the offspring have reached late adolescence

Table 1. A Sample of Long-Term Behavioral and Cognitive Dysfunctions as Identified in Developmental Immune Activation Models in Rats and Mice

		Behavioral and Cognitive Abnormalities in Adult Offspring Born to Immune-Challenged Mothers								
Immunogen	Principal Mode of Action	Sensorimotor Gating	Selective Attention	Social Behavior	Exploratory Behavior	Working Memory	Cognitive Flexibility	Sensitivity to Psychotomimetic Drugs	Methodological Advantages	Methodological Disadvantages
Influenza	Broad innate and adaptive antiviral immune response, including production of cytokines and antibodies, and activation of B- and T- cells after maternal intranasal application.	↓	ND	↓	↓↓	ND	ND	↑	Full spectrum of immune response normally induced by infections, including antibody production	Stringent biosafety precautions necessary No easy control of immune response intensity and duration
Poly(I:C)	Recognition by TLR3 and induction of cytokine-associated viral-like acute phase response after systemic maternal administration.	↓↓↓	↓↓↓	↓↓	↓↓	↓↓↓	↓↓↓	↑↑↑	No stringent biosafety precautions necessary Strictly limited duration of immune response Easy control of (cytokine-associated) immune response intensity	Limited immune response spectrum
LPS	Recognition by TLR4 and induction of cytokine-associated bacterial-like acute phase response after systemic maternal administration.	↓↓	ND	↓↓	↓↓	ND	ND	↑	No stringent biosafety precautions necessary Strictly limited duration of immune response Easy control of (cytokine-associated) immune response intensity	Limited immune response spectrum Marked fetal losses due to spontaneous abortion (high doses)
Turpentine	Local tissue damage, recruitment and activation of immune cells, and secretion of pro-inflammatory cytokines after maternal intramuscular injection.	↓	ND	ND	ND	ND	ND	↑	No stringent biosafety precautions necessary Strictly limited duration of inflammatory response Maternal localization of maternal inflammatory response	Limited immune response spectrum Muscular injury/trauma
IL-6	Induction of fever and acute phase responses after systemic maternal administration.	↓	↓	↓	↓	ND	ND	ND	No stringent biosafety precautions necessary Strictly limited duration of immune response Easy control of immune stimulus intensity	Limited immune response spectrum

The models are based on prenatal exposure to human influenza virus, the viral mimic polyriboinosinic-polyribocytidilic acid (poly[I:C]), the bacterial endotoxin lipopolysaccharide (LPS), the locally acting inflammatory agent turpentine, and the pro-inflammatory cytokine interleukin (IL)-6. Downward and upward arrows indicate an impairment or enhancement of the particular phenotype, respectively. The number of arrows reflects the number of replications by independent research institutes, with three arrows signifying three or more independent replications. Data from Meyer *et al.* (24) and Meyer and Feldon (25,32). Note that the precise timing and dosing of the prenatal immunogens might significantly influence the nature and/or severity of the outlined functional changes [not indicated in the table; for a detailed discussion see Meyer *et al.* (4,24,39)]. Some of the methodological advantages and disadvantages of each model are also summarized.

ND, not determined; TLR, transmembrane protein toll-like receptor.

or early adulthood (41–44). This maturational delay is indicative of a progression of pathological symptoms from pubescence to adulthood, which is consistent with the post-pubertal onset of full-blown psychotic behavior in schizophrenia and related disorders (45).

Numerous theories have been put forward to explain why most subjects at risk for schizophrenia develop full-blown psychotic disease only after reaching late adolescence or early adulthood. One prevalent hypothesis suggests that this delayed clinical course might be related to the functional maturation of intracortical connectivity, especially within prefrontal-temporolimbic cortical pathways (46). Other theoretical accounts of this maturational delay focus on the influence of (sex-dependent) hormonal refinements occurring during the periadolescent stage of life (47) and/or interactions with exposure to stressful situations and associated changes in the stress-response system (48). The prenatal poly(I:C) model provides a unique opportunity to identify the developmental character and molecular processes of neuropathological changes across postnatal brain maturation (32,49). Such efforts are highly desirable, because therapeutic interventions during the periadolescent life span might represent an effective strategy to reduce the incidence of or even prevent the emergence of multiple brain dysfunctions in high-risk subjects with a (immune-mediated) neurodevelopmental predisposition to adult mental illness. Experimental efforts toward this direction are underway, and the prenatal poly(I:C) model has already provided initial promising data suggesting that periadolescent treatment with reference antipsychotic or antidepressant drugs can successfully block at least some of the behavioral and brain abnormalities in prenatally poly(I:C)-exposed offspring (50–53).

Another important feature of the prenatal poly(I:C) model is that the severity of the long-term brain and behavioral changes are dependent on the intensity of the cytokine-associated immune reaction (33,54). The apparent impact of the precise immune stimulus intensity suggests that there is a threshold of (viral-like) immune activation that is required to induce long-term brain and behavioral pathology in the offspring. The dose-dependent nature of the prenatal poly(I:C)-induced effects parallels findings indicating that more severe forms of prenatal immune abnormalities are associated with more intense structural brain abnormalities in offspring affected with schizophrenia (55). Another feasible assumption derived from such dose-response effects is that prenatal (viral-like) infection enhances the risk of schizophrenia only if the infectious process is associated with relatively strong immunological reactions in the maternal/fetal compartments and/or if this early-life immunological insult takes place in conjunction with additional genetic or environmental risk factors (see following).

Finally, the prenatal poly(I:C) model is also very useful to test the hypothesis that the vulnerability to infection-induced neurodevelopmental abnormalities differs between distinct stages of fetal development. This can be achieved by comparing the effects of prenatal poly(I:C) at distinct gestational stages relative to corresponding prenatal control treatment (39,56–58). The poly (I:C)-induced immune reactions in the maternal host are time-limited, ranging from 24 to 48 hours, depending on the precise dose used (37), thus allowing the experimenter to precisely time the maternal immune response according to specific periods of fetal development. Such experimental investigations seem highly relevant to address some of the ongoing debates as to whether the strength of the association between prenatal maternal infection and enhanced schizophrenia risk is dependent on the precise prenatal timing (4).

The Present, Part 2: Models of Bacterial-Like Immune Activation by Lipopolysaccharide

Maternal administration of the bacterial endotoxin lipopolysaccharide (LPS) is a widely used model system to mimic an innate acute phase response to bacterial infection in the absence of live bacteria exposure. LPS is an inherent cell wall component of gram-negative bacteria, which is recognized mainly by the pathogen recognition receptor transmembrane protein toll-like receptor 4 (36). Upon binding to toll-like receptor 4, LPS stimulates the expression of a wide array of innate immune responses that include the synthesis and release of various pro-inflammatory cytokines (36). There are some notable similarities between the cytokine-associated inflammatory responses triggered by LPS and poly(I:C) (36,38). Therefore, it might not seem surprising that prenatal LPS treatment, similarly to poly(I:C), precipitates a number of behavioral and neurochemical changes relevant to schizophrenia and related psychotic illnesses (Table 1).

Despite the apparent similarities between the LPS- and poly (I:C)-induced effects, there are also some noticeable differences between the two models with respect to the nature of brain and behavioral changes. For example, early prenatal poly(I:C) treatment in mice has been shown to increase midbrain dopamine cells (44), whereas prenatal LPS exposure leads to the opposite effect (59). Prenatal LPS exposure in rhesus monkey has also been found to cause a significant increase in global white matter volume (60), whereas an opposite pattern (i.e., decreased white matter volume) has been noted in rhesus monkey offspring born to influenza-infected mothers (26). Such differences in the long-term outcomes between prenatal exposures to bacterial-like and viral/viral-like immunogens might be taken to support the idea that different pathogens can induce a distinct set of neuroimmune abnormalities across brain development.

It remains to be determined whether such differences can be explained by the differential immune signatures and pathophysiological responses triggered by different immunogens. Unlike LPS, for example, poly(I:C) is a potent inducer of type I IFNs that stimulate antiviral immune responses (38). By contrast, LPS is more effective in stimulating the production and secretion of TNF-α from innate immune cells such as macrophages (61). The differential effects on TNF-α might be a reason why LPS is more potent than poly(I:C) in triggering anorexia, lethargy, and febrile responses (62). In view of the strong apoptotic activity of TNF-α (63), maternal LPS exposure might also be more effective in inducing neurotoxic effects in the fetal brain compared with maternal poly(I:C) treatment (64). Indeed, maternal or intrauterine exposure to LPS has been widely used as an experimental model system for the induction of perinatal white and gray matter damage in relation to cerebral palsy and other developmentally acquired neurological conditions (64–66).

The Present, Part 3: Models of Local Inflammation and Exposure to Individual Cytokines

There have been recent attempts to explore whether local maternal inflammation during pregnancy is sufficient to induce long-term brain and behavioral changes in the offspring. One promising model is based on maternal intramuscular injection of turpentine oil (67–69). After its intramuscular injection, turpentine remains confined at the site of administration and locally causes tissue damage, recruitment and activation of immune cells, and secretion of pro-inflammatory cytokines (67–69). This experimental approach offers the opportunity to study the effects of

circulating inflammatory mediators that are solely produced by the maternal immune system. Hence, in contrast to poly(I:C)- or LPS-based models of systemic immune activation (70,71), placental secretion of inflammatory markers is minimal, and this readily facilitates the delineation of the relative contribution of maternally produced versus placenta-derived inflammatory factors in the link between prenatal inflammation and abnormal brain and behavioral development (67–69). Intriguingly, maternal turpentine treatment is effective in inducing long-term behavioral and pharmacological changes in the offspring, some of which are highly similar to the pathologies found after prenatal exposure to other immune activating agents (Table 1). These findings provide further support for the hypothesis that induction of maternal inflammatory responses might be a key factor mediating the association between maternal infection during pregnancy and altered behavioral development in the offspring. Moreover, given that intramuscular injection of turpentine causes localized tissue damage, the findings from this model might be taken to encourage human epidemiological studies exploring potential associations between maternal physical trauma and increased risk of neurodevelopmental disorders in the offspring.

Another valuable approach to delineate the role of cytokine-associated mechanisms is to treat pregnant animals with specific cytokines. This approach has been successfully implemented both in rats and mice (72,73). The existing data indicate that the inflammatory cytokine IL-6 might be a crucial immunological mediator of the link between maternal immune activation and altered brain development. Indeed, administration of exogenous IL-6 to pregnant animals is sufficient to induce long-lasting structural and functional abnormalities in the adult offspring, some of which are highly comparable to those induced by prenatal exposure to other immune activating agents such as poly(I:C) (72,73). Moreover, when IL-6 is eliminated from the maternal immune response by genetic interventions or with IL-6 blocking antibodies, maternal immune challenge by poly(I:C) is no longer efficient in inducing behavioral maldevelopment in the resulting offspring (72). Prenatal exposure to other proinflammatory cytokines alone, including IL-1β, IFN-γ, or TNF-α, seems to be insufficient to precipitate similar behavioral deficits in the adult animals; and co-administration of soluble IL-1β or IFN-γ receptor antagonist to pregnant dams does not prevent the behavioral deficits caused by prenatal poly(I:C) exposure (72).

It remains to be further elucidated why IL-6 might be a key cytokine in mediating the link between prenatal immune challenge and altered brain development. One parsimonious explanation might be that IL-6 is readily capable of crossing the placental barrier, whereas other inflammatory mediators such as IL-1β and TNF-α display only minimal transplacental transfer (74). Interestingly, IL-6 exerts some noticeable anti-inflammatory effects in addition to its known pro-inflammatory functions (75). The disruption of the balance between pro- and anti-inflammatory signaling in prenatal life might thus represent an important mechanism precipitating changes in brain and behavioral development (76). Taken together, it seems that the nature and/or severity of neuropathological outcomes after prenatal infection and/or inflammation might be, at least in part, influenced by the specificity of cytokine-associated immunological reactions. Additional research toward this direction is highly warranted, because the identification of specific key mechanisms might offer an effective strategy to attenuate or even prevent the neurodevelopmental sequelae associated with prenatal infection.

The Future: Deconstructing the Phenotypes and Broadening the Concepts

It seems no longer a matter of debate that the etiology of multifaceted neuropsychiatric disorders such as schizophrenia is multifactorial. With the establishment of more sophisticated genetic techniques and epidemiological approaches, the list of potential candidate genetic and environmental risk factors for schizophrenia is constantly rising (77,78). Furthermore, it is becoming increasingly evident that seemingly remote disorders such as schizophrenia, autism, attention-deficit/hyperactivity disorder, and major depression share considerable amounts of risk factors and brain dysfunctions (79–82). The presence of shared genetic and environmental risk between those illnesses has led to the proposal that they might lie along a continuum of genetically and environmentally induced neurodevelopmental causality (82,83). This concept has a number of implications for those of us who are attempting to study disease-relevant neurobiological and behavioral correlates in animal models. First and foremost, animal researchers should not aim for an animal model that could possibly recapitulate the full spectrum of behavioral symptoms associated with a complex brain disorder such as schizophrenia. This is especially true when the model is based on one particular genetic or environmental manipulation only. Such single risk-factor models should rather be expected to induce a restricted set of brain and behavioral changes, and those changes should not be canalized or fitted into one specific neuropsychiatric disease entity (84).

Some of these considerations have encouraged animal researchers to develop translational models that incorporate multiple etiologically relevant risk factors (85,86). On the basis of the role of prenatal infection in schizophrenia, there have been recent attempts to explore the cumulative impact of immune-related environmental challenges and distinct genetic abnormalities in the disruption of brain and behavioral development. The rationale for these attempts is given by epidemiological findings suggesting that prenatal infections seem to have rather modest effects in large populations in spite of their relatively frequent occurrence (87). It has therefore been proposed that early-life immune challenge might unfold its neuropathological impact primarily in genetically predisposed subjects (88). Another feasible scenario is that initial exposure to a prenatal environmental insult, such as infection, can render the offspring more vulnerable to the pathological effects of a second postnatal stimulus, such as exposure to traumatizing experiences or chronic consumption of drugs of abuse (89).

Rodent prenatal immune activation models seem highly suitable for these kinds of gene–environment or environment–environment interaction studies (Figure 1). With the maternal poly (I:C) administration model in mice, it has recently been shown that the brain and behavioral consequences of (mild and physiologically relevant) prenatal immune activation are markedly exacerbated in offspring with genetic predisposition to neurodevelopmental abnormalities induced by mutant expression of disrupted-in-schizophrenia 1 (40,90) or by mutations in the dopamine-related transcription factor Nurr1 (91). Intriguingly, the combination of such genetic manipulations and prenatal immune activation does not only produce additive effects but further leads to behavioral disturbances that are not manifest after exposure to either manipulation alone (40,90,91). Our laboratory has recently developed an environmental "two-hit" model, in which exposure to physiologically relevant dose of

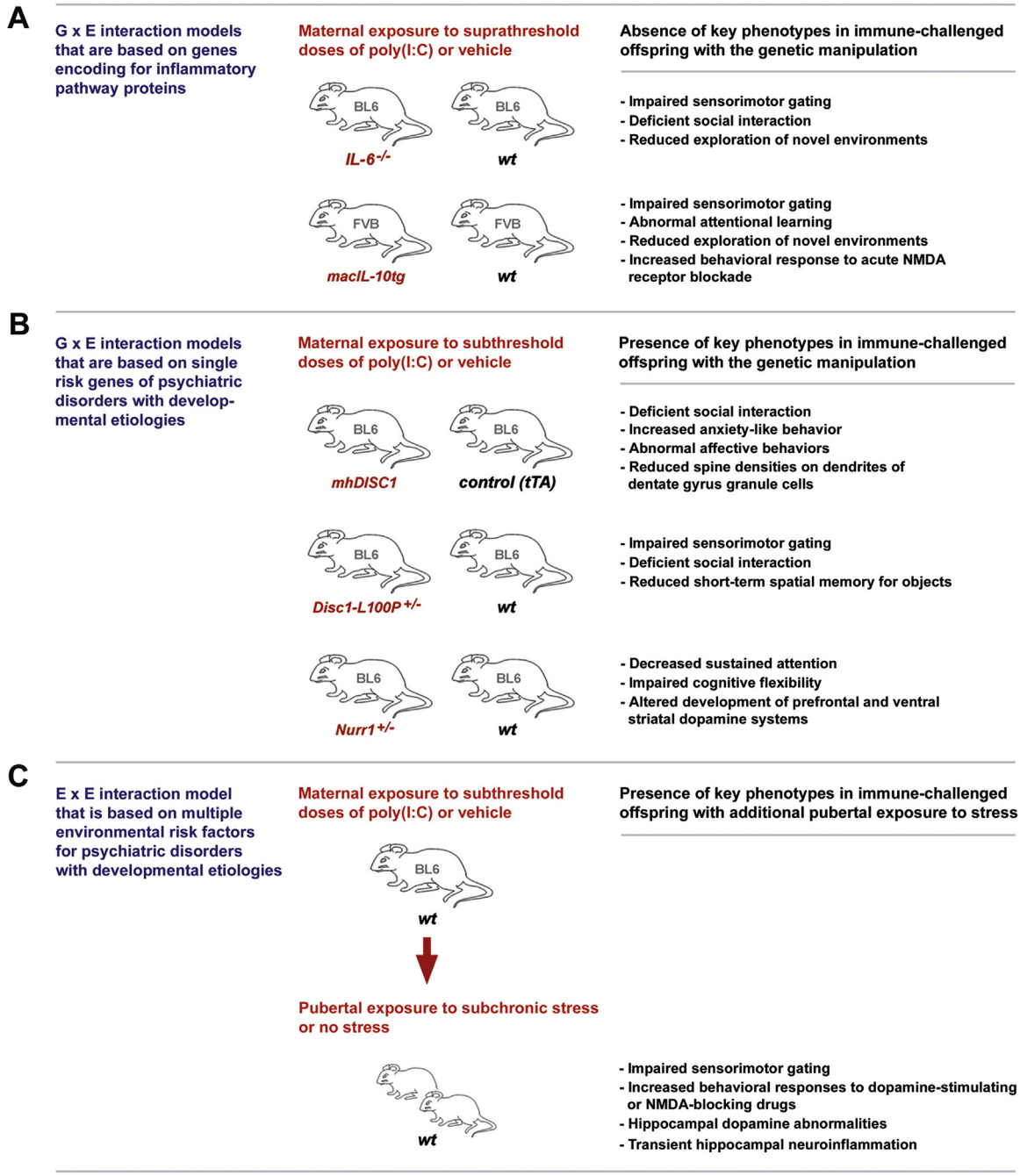

Figure 1. A summary of existing gene–environment (G × E) and environment–environment (E × E) interaction models using prenatal polyriboinosinic-polyribocytidilic acid (poly[I:C]) exposure in mice. Depending on the model, poly(I:C) is given to pregnant mice at subthreshold or suprathreshold doses, respectively, which is efficient or inefficient to induce multiple brain and behavioral abnormalities in the offspring in the absence of additional genetic or environmental manipulations. These models have been established in inbred C57BL6 (BL6) or FVB strains of mice. **(A)** G × E interaction models that are based on genes encoding for inflammatory pathway proteins (72,76). These models compare the effects of suprathreshold maternal poly(I:C) exposure in wild-type (wt) mice relative to mice with genetic interleukin-6 deficiency (IL-6−/−) or macrophage-specific overexpression of interleuckin-10 (macIL-10tg). **(B)** G × E interaction models that are based on single risk genes of psychiatric disorders with developmental etiologies (40,90,91). These models compare the effects of subthreshold maternal poly(I:C) exposure in wt or tetracycline-controlled transactivator protein (tTA) control mice relative to mice with mutant human DISC1 expression (mhDISC1), DISC1 point mutation (Disc1-L100P+/−), or genetic deficiency in Nurr1 (Nurr1+/−). **(C)** An E × E interaction model that is based on multiple environmental risk factors for psychiatric disorders with developmental etiologies (92). This model compares the effects of subthreshold maternal poly(I:C) exposure in wt offspring with or without additional exposure to subchronic stress in pubescence. NMDA, *N*-methyl-D-aspartate.

maternal poly(I:C) treatment served as the first hit and exposure to sub-chronic stress in pubescence served as the second hit (92). In this model, mild prenatal immune activation and peripubertal stress caused synergistic effects in the development of specific behavioral abnormalities such as sensorimotor gating deficiency and enhanced sensitivity to psychotomimetic drugs (92). Neither

immune activation alone nor stress alone affected these behavioral functions in adulthood, so that abnormalities in these domains became evident only after combined exposure to the two environmental factors (92). Hence, prenatal infection can act as a "disease primer" that increases the vulnerability of the offspring to the detrimental neuropathological effects of other environmental insults such as peripubertal stress.

Taken together, animal models might critically help to identify complex interactions between discrete genetic and environmental risk factors in the development of chronic mental illnesses. These novel approaches hold promise especially for psychiatric disorders with neurodevelopmental components, considering how little we understand about the disruption of brain development induced by combined effects of multiple genetic or environmental adversities.

Concluding Remarks

Modeling the epidemiological association between prenatal immune challenge and altered brain and behavioral development in rodent systems has produced an astonishing amount of experimental data supporting a role of immune-mediated neurodevelopmental abnormalities in major psychiatric illnesses. Many of the models can mimic a broad spectrum of behavioral, cognitive, and pharmacological abnormalities relevant to schizophrenia and beyond. Perhaps one of the most important features of prenatal immune action models is that they are "neurodevelopmental disruption models": they allow a multifaceted, longitudinal monitoring of the disease process as it unfolds during the course of neurodevelopment from prenatal to adult stages of life. Moreover, they do not rely on any presumption of the neuronal substrates of a specific disorder, and therefore they offer an unbiased way to identify etiopathological processes underlying the changes in neurodevelopmental trajectories and behavioral functions after exposure to prenatal adversities such as infection. Quite surprisingly, however, prenatal immune activation models have thus far largely ignored the (pathological) processes occurring during the early postnatal period. Indeed, the investigation of physiological, behavioral, and neuroanatomical functions at neonatal or early juvenile stages of life is relatively rare in the existing models (93,94). It would seem highly important to gain knowledge about possible disturbances in early neurobehavioral functions, because subjects who later go on to develop chronic mental illness such as schizophrenia often show (subtle) cognitive, motor, and social disabilities during the premorbid phase of the disease (5,45).

Related to this, it is highly conceivable that prenatal immune activation models are likely to be relevant for a number of brain disorders with neurodevelopmental components (66). Epidemiological support for this notion is manifold: prenatal maternal infection and/or inflammatory processes have also been linked to —besides schizophrenia—increased risk of autism (95,96), attention-deficit/hyperactivity disorder (97), and cerebral palsy (98,99). As pointed out by Harvey and Boksa (66), one needs to consider that prenatal exposure to infection (in animal models) is a general vulnerability factor for neurodevelopmental disorders rather than a disease-specific risk factor. The findings derived from the recently established models, in which prenatal poly(I:C) exposure is combined with a specific genetic (40,90,91) or additional environmental (92) factor, strongly support this concept. Hence, the adverse effects induced by prenatal infection should be generally considered as an early entry into the neuropsychiatric route, but the specificity of subsequent disease or symptoms is likely to be strongly influenced by the genetic and environmental context in which the prenatal infectious process occurs.

The epidemiological literature reporting enhanced risk of chronic mental illnesses after early-life exposure to infection and/or inflammation is still evolving, and so are the attempts to model these associations in experimental animals. McGrath and Richards (23) correctly point out that there is a "need to build shared discovery platforms that encourage greater cross-fertilization between schizophrenia epidemiology and basic neuroscience research." The experimental models discussed in the present review represent an important step toward this direction. It is the continual integration of epidemiological and experimental work that will truly further our understanding of how prenatal infection and inflammation increases the risk of neurodevelopmental brain disorders.

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