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The Poly(I:C)-induced maternal immune activation model in preclinical neuropsychiatric drug discovery

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ABSTRACT

Increasing epidemiological and experimental evidence implicates gestational infections as one important factor involved in the pathogenesis of several neuropsychiatric disorders. Corresponding preclinical model systems based upon maternal immune activation (MIA) by treatment of the pregnant female have been developed. These MIA animal model systems have been successfully used in basic and translational research approaches, contributing to the investigation of the underlying pathophysiological mechanisms at the molecular, cellular and behavioral levels. The present article focuses on the application of a specific MIA rodent paradigm, based upon treatment of the gestating dam with the viral mimic polyinosinic–polycytidilic acid (Poly(I:C)), a synthetic analog of double-stranded RNA (dsRNA) which activates the Toll-like receptor 3 (TLR3) pathway. Important advantages and constraints of this animal model will be discussed, specifically in light of gestational infection as one vulnerability factor contributing to the complex etiology of mood and psychotic disorders, which are likely the result of intricate multi-level *gene* × *environment* interactions. Improving our currently incomplete understanding of the molecular pathomechanistic principles underlying these disorders is a prerequisite for the development of alternative therapeutic approaches which are critically needed in light of the important drawbacks and limitations of currently available pharmacological treatment options regarding efficacy and side effects. The particular relevance of the Poly(I:C) MIA model for the discovery of novel drug targets for symptomatic and preventive therapeutic strategies in mood and psychotic disorders is highlighted in this review article.

Contents

Abbreviations: ASD, autism spectrum disorders; DISC1, disrupted in Schizophrenia 1 gene; dsRNA, double-stranded RNA; LPS, lipopolysaccharide; MDD, major depressive disorder; MIA, maternal immune activation; NMDA, *N*-methyl-D-aspartate; Poly(I:C), polyinosinic:polycytidylic acid; SSRI/SNRI, selective serotonin or norepinephrine reuptake inhibitor; TLR, toll-like receptor.

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1. Introduction

Strong epidemiological and experimental evidence suggests early life adversity, including the pre-, peri- and early postnatal period, as a common factor involved in the pathogenesis of some of the most debilitating mental illnesses, including mood and psychotic disorders (Brown & SES, 2002; Fortier et al., 2007; Meyer et al., 2007; Meyer et al., 2009b; Atladottir et al., 2010; Bitanihirwe et al., 2010; Boksa, 2010; Brown & DEJ, 2010; Piontkewitz et al., 2012; Vuillermot et al., 2012; Zhang et al., 2012; Burt et al., 2013; Khan et al., 2014; Meyer, 2014b). These two complex neuropsychiatric disorders are linked at several levels, including the parallel presentation of psychotic and depressive symptoms frequently observed in patients and emerging evidence for overlapping etiological and pathophysiological features (see for review Buckley et al., 2009). Specifically, stressful events during embryogenesis are hypothesized to have deleterious consequences on fetal brain development (Meyer et al., 2009b; Piontkewitz et al., 2012), which may contribute to the manifestation of mental illness later in life (Koenig et al., 2002; Winter et al., 2009; Boksa, 2010; Lin et al., 2012; Khan et al., 2014). Recently, growing support for gestational infection stress as one particular condition impinging on the developing brain and associated with neurobehavioral alterations in adulthood, has been obtained from epidemiological studies as well as from analyses in experimental animal models (see for review: Meyer et al., 2007 #539; Rapoport et al., 2005; Meyer et al., 2009b; Boksa, 2010; Markham & KJI, 2011; Khandaker et al., 2013).

The normal course of fetal development requires a specific balance between the maternal and fetal environments of constitutively expressed cytokines – small pleiotropic signaling molecules released as part of the innate immune response – with the placenta constituting the structural interface for maternal–fetal–immune interaction (Mehler & Kessler, 1998; Cannon et al., 2002; Deverman & Patterson, 2009; Dickerson & Bilkey, 2013; Garay et al., 2013). In the case of hemochorial placentation, the type of placentation occurring in mammals including humans and rodents, the placenta allows for direct contact between the maternal and fetal compartments (Colucci et al., 2011), and fetal syntiotrophoblast cells are exposed to mediators of the maternal immune response (Moffett & Loke, 2006). While under physiological conditions, this process is tightly controlled (Munn et al., 1998), maternally derived cytokines and chemokines may excessively permeate the fetal compartment in cases of severe maternal immune challenge (Fig. 1). As a consequence of the fetal immune system not being prepared to adequately respond to severe proinflammatory influences, the cytokine equilibrium in the developing brain is thrown off-balance (Welberg et al., 2000; Seckl, 2004; Mueller & Bale, 2008). This cytokine imbalance can compromise the molecular, structural and functional integrity of the developing brain with long-lasting consequences contributing to the development of neuropsychiatric disturbances later in life (Zhao & JPS, 1998; Patterson, 2007; Meyer et al., 2009b; Burd et al., 2012).

Epidemiological studies have repeatedly confirmed a relationship between maternal immune activation (MIA) and psychiatric disorders such as schizophrenia (Brown & SES, 2002; Buka et al., 2008; Brown & DEJ, 2010) (Table 1), autism-spectrum disorder (ASD) (Martin et al., 2008; Fox et al., 2012), as well as neurological impairments including cerebral palsy (Rasiah Vigneswaran et al., 2003; Folkerth, 2005) in adult offspring. The long-lasting impact of gestational infection on offspring brain structure and function is further evidenced by analyses of post-mortem tissue samples of exposed individuals diagnosed with psychiatric disorders schizophrenia, ASD, bipolar disorder and depression (Lewis & Levitt, 2002; Patterson, 2007; Jaaro-Peled et al., 2009; Brown & DEJ, 2010). Epidemiological examinations of large population samples are a potent tool for the investigation of associative relationships between certain environmental conditions, prenatal infections, and disease risk, the development of neuropsychiatric disorders. However, testing causal associations and elucidating the underlying cellular and molecular pathophysiological mechanisms – a prerequisite for the development of novel treatment options – are dependent on the establishment and use of animal models.

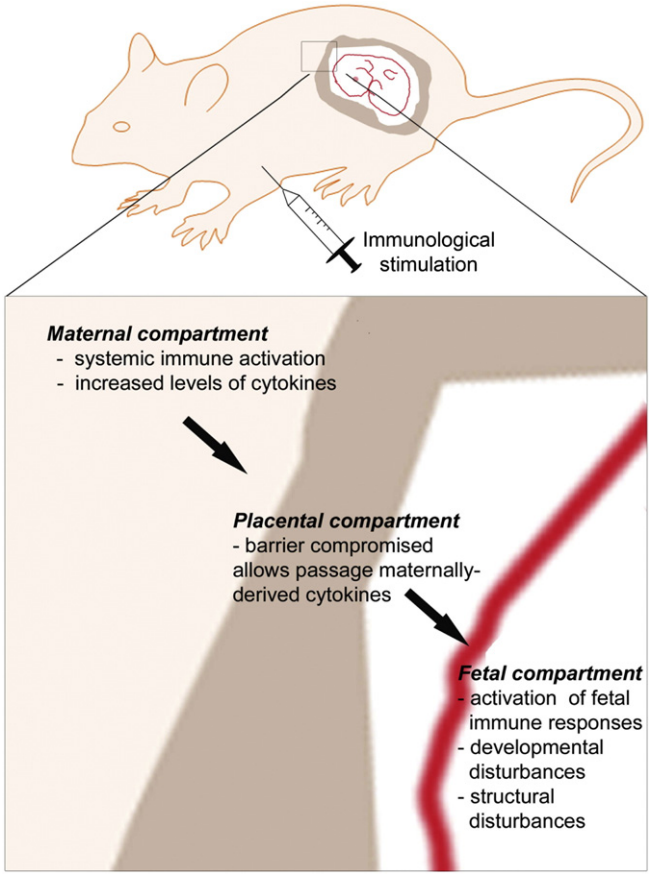

Fig. 1. The rodent maternal immune activation model. Gestational infection is mimicked by immunological stimulation of the gestating dam with immune-stimulating agents such as Poly(I:C). Responses in the maternal compartment include systemic immune activation characterized by increased levels of proinflammatory cytokines. Consequently, the integrity of the placental barrier becomes compromised, allowing entrance of maternally-derived cytokines into the fetal circulation and inducing inflammatory responses in the developing fetus, including the brain. This leads to structural and developmental disturbances associated with various neuropsychiatric diseases such as schizophrenia and depression.

With regard to the effects of gestational infection on adult offspring brain function and behavioral phenotypes, specific animal models of MIA based upon administration of immunogenic substances to the pregnant female have been developed. The most commonly used approaches rely on mimicking maternal infection by treatment with the bacterial endotoxin lipopolysaccharide (LPS) and the double-stranded RNA (dsRNA) analog polyinosinic:polycytidylic acid (Poly(I:C)) (Fig. 1). While LPS and Poly(I:C) elicit distinct molecular profiles – targeting the toll-like receptor (TLR) 4 and TLR3 pathways respectively – both MIA paradigms have been successfully used to establish animal models for some of the most common and debilitating neuropsychiatric disorders, including schizophrenia, autism and depression (Fatemi et al., 1999; Fatemi et al., 2002a, 2002b; Fatemi et al., 2002b; Smith et al., 2007; Garbett et al., 2012; Dickerson & Bilkey, 2013; Bauman et al., 2014; Khan et al., 2014). Despite continuous efforts, the neurobiological basis of these severe mental illnesses, which compromise the quality of life of patients and their families as well as posing significant socioeconomic burden on society (Kessler et al., 2003), remain incompletely understood currently available pharmacotherapeutic options present with major limitations: they provide relief from only some of the symptoms and fail to cure the respective disorders, are effective only in a limited number of affected patients,

Table 1
Human studies describing the role of maternal immune activation in neuropsychiatric diseases.

Neuropsychiatric disorder(s)	Reference	Study design	Pathogen(s)/Pathogenic mechanism(s)	Results	Effect of infection on risk for relevant neuropsychiatric disorder(s)
Affective disorders	Brown et al., 1995	Ecological study	Influenza virus	Reduced risk of developing affective disorders after putative exposure to influenza epidemic	⇓
Major depression	Machon et al., 1997	Ecological study	Influenza virus	Increase in major depression diagnoses after putative exposure to influenza epidemic	⇑
Major depression	Mino et al., 2000	Ecological study	Influenza virus	No effect found	⇔
Major depression	Pang et al., 2009	Nested case–control study	Various viral agents (total effect analyzed)	No effect found	⇔
Schizophrenia/affective psychotic disorders	Takei et al., 1993	Ecological study	Influenza virus	Increased schizophrenia diagnoses after putative exposure to influenza epidemic; decrease in affective psychotic disorder diagnoses	⇑ (SCZ) ⇓ (affective psychotic disorder)
Schizophrenia and depressive illness	Cannon et al., 1996	Follow-up on cohort study	Influenza virus	Increased risk for depressive illness among exposed individuals; no significant effect on schizophrenia diagnoses found	⇑ (MDD) ⇔ (SCZ)
Schizophrenia and affective psychosis	Cahill et al., 2002	Ecological study	Poliovirus	No effect found	⇔
Schizophrenia	Watson et al., 1984	Ecological study	Various infectious diseases	Increased risk for schizophrenia in individuals with birth years directly following time periods of high prevalence of infectious diseases	⇑
Schizophrenia	Mednick et al., 1988	Ecological study	Influenza virus	Increased risk for schizophrenia in individuals exposed to influenza during gestation	⇑
Schizophrenia	Torrey et al., 1988	Ecological study	Various viral agents (total effect analyzed)	Increased risk for schizophrenia after putative exposure to measles, varicella zoster, polio; influenza showed effect just below significance level; no effect of rubella or mumps found	⇑ (measles, varicella zoster, polio) ⇔ (rubella, mumps)
Schizophrenia	Barr et al., 1990	Ecological study	Influenza virus	Increased schizophrenia diagnoses in individuals exposed to periods of high incidence of influenza during gestation	⇑
Schizophrenia	O'callaghan et al., 1991	Ecological study	Influenza	Increase in births of schizophrenic individuals 5 months after peak infection prevalence	⇑
Schizophrenia	Crow & done, 1992	Cohort study	Influenza virus	No effect found	⇔
Schizophrenia	Adams et al., 1993	Ecological study	Influenza virus	Increased schizophrenia diagnoses after influenza epidemics in three cohorts of patients	⇑
Schizophrenia	Susser et al., 1994	Ecological study	Influenza virus	No effect found	⇔
Schizophrenia	Suvisaari et al., 1999	Ecological study	Poliovirus	Increased schizophrenia diagnoses in individuals exposed to periods of high incidence of poliomyelitis during gestation	⇑
Psychotic disorders	Brown et al., 2000	Follow-up on cohort study	Rubella virus	Increased risk for nonaffective psychosis among individuals exposed to rubella during gestation	⇑
Psychotic disorders	Buka et al., 2001	Nested case–control study	Analysis of antibodies in maternal serum at birth	Association between elevated maternal levels of IgG, IgM and antibodies against HSV-2 (but not against several other pathogens) and schizophrenia diagnoses in offspring	⇑ (HSV-2)
Schizophrenia	Limosin et al., 2003	Case–control study	Influenza virus	Increased risk for schizophrenia in individuals exposed to influenza during gestation	⇑
Schizophrenia	Brown et al., 2004	Nested case–control study	Influenza virus	Increased risk for schizophrenia in individuals exposed to influenza during gestation	⇑
Schizophrenia	Brown et al., 2005	Nested case–control study	*Toxoplasma gondii*	Increased risk for schizophrenia spectrum disorders in subjects with high maternal levels of *T. gondii* antibody	⇑
Schizophrenia	Babulas et al., 2006	Cohort study	Maternal genital/ reproductive infections	Increased risk for schizophrenia and schizophrenia spectrum disorders in individuals exposed during the periconceptional period	⇑
Schizophrenia	Mortensen et al., 2007	Case–control study	*Toxoplasma gondii*	Increased risk for schizophrenia in subjects with high maternal levels of *T. gondii* IgG antibody	⇑
Psychotic disorders	Buka et al., 2008	Nested case–control study	Herpes simplex virus	Increased risk of developing psychoses in Offspring of mothers seropositive for herpes simplex	⇑
Schizophrenia	Sorensen et al., 2009	Cohort study	Various bacterial agents (individual/grouped effects analyzed)	Increased risk for schizophrenia in individuals exposed to various bacterial pathogens during gestation	⇑
Schizophrenia	Ellman et al., 2010	Case–control study	IL-8	Increased risk for presenting neuroanatomical changes that have been previously linked to schizophrenia among cases exposed to IL-8 in utero	⇑

and treatment is frequently associated with a range of unpleasant side effects, severely compromising patient compliance rates (Rush et al., 2006; Warden et al., 2007; Gaynes, 2009).

In the case of major depressive disorder (MDD), the dominant pharmacological treatment approach involves the use of selective serotonin or norepinephrine reuptake inhibitors (SSRIs/SNRIs) as well as tricyclic

antidepressants (Davidson, 2010). In more resistant cases, monoamine oxidase inhibitors (MAOIs) are also prescribed, though some argue these continue to be underused (Shulman et al., 2013). Besides drug therapy, non-pharmacological approaches including various forms of psychological interventions such as cognitive behavioral therapy or interpersonal psychotherapy, are known to show considerable efficacy (see for review: Cuijpers et al., 2008; Gloaguen et al., 1998; van Hees et al., 2013). For medium and severe chronic depression, the most successful treatment is thought to involve a combination of medication and psychotherapy (Pampallona et al., 2004; de Maat et al., 2007; Cuijpers et al., 2009). In response to the urgent need for the development of rapidly acting antidepressants, novel treatment alternatives including the use of deep transcranial magnetic stimulation (TMS) of the anterior cingulate cortex and the application of the *N*-methyl-D-aspartate (NMDA) antagonist ketamine are emerging (Mayberg et al., 2005; Machado-Vieira et al., 2009). Currently, due to its relatively modest side effects and high therapeutic potential, TMS is proposed to replace electroconvulsive therapy, the most ancient psychiatric intervention in MDD (Micallef-Trigona, 2014).

In schizophrenia, on the other hand, available treatments are mainly effective in alleviating the positive symptoms, including delusions and hallucinations, with a major lack of treatment options available to address the negative (mainly avolition, anhedonia and reduced affect) and cognitive symptoms of the disease (Pratt et al., 2012). Commonly applied therapeutic strategies rely on the use of first-generation or second-generation antipsychotics (FGA/SGAs), all of which directly and/or indirectly target the dopamine receptor type 2 (D2) (Pratt et al., 2012). Routine clinical approaches are either based upon monotherapy with antipsychotics or a combination treatment with other pharmacological (often antidepressant) or non-pharmacological (mainly psychotherapy) treatments (Kane et al., 2003). While the possibility to medically reduce the burdensome positive symptoms of schizophrenia is immensely beneficial for the afflicted patients, the alleviation of negative and cognitive symptoms still represents unmet important therapeutic needs. However, the discovery of novel therapeutic avenues is largely dependent on improving our understanding of the intricate neurobiological processes underlying the symptoms experienced by affected patients which, importantly, builds upon the availability of useful and trustworthy animal models. Considering the constraints in the therapeutic potential of most commonly used drug treatments and the limited progress in the discovery and implementation of alternative approaches, the development of entirely new preclinical model systems emerges as an important prerequisite for future developments. These models should have a high degree of construct validity, reflecting identified genetic and/or environmental factors contributing to the pathophysiology of the disease, rather than predicting the efficacy of currently available drugs which do not address a considerable part of the symptomatic spectrum of the disease.

Here, animal models of gestational infection constitute an exciting advance, since they reproduce in an experimentally amenable setting the contribution of particular aspects of adverse early life events, based upon infectious stress, a known risk factor for the development of mood and psychotic disorders (Table 1). The present review strives to provide an overview of the use of animal models for the experimental assessment of the role of MIA in the pathophysiology of these disorders, focusing on the Poly(I:C) paradigm and its utility for drug discovery.

2. Animal models of maternal immune activation in neuropsychiatric research

Animal models of complex diseases of the human mind are always subject to particular scrutiny, within the scientific community as well as the general public. Attempting to recapitulate in laboratory animals, mainly rodents, behavioral features which in part (such as hallucinations, delusions, suicidal thoughts or feelings of worthlessness) are considered inherent to the human species and are not ascertainable in other animals, represents a major challenge. However, the pathophysiological complexity of most psychiatric disorders, involving a plethora of *gene* × *environment* interactions, further underscores the important role of relevant and reliable animal models. These models serve as experimental tools for the investigation of the pathophysiological mechanisms involved, a prerequisite for the identification of novel therapeutic strategies. Making no pretense to reproduce in its entirety the spectrum of neuropathological features giving rise to the multitude of symptoms presented in the patient population, a single animal model can have its usefulness — when properly validated according to established quality criteria.

The classic framework for the assessment of validity of animal models is built upon the three major pillars of construct, face and predictive validity (Willner, 1997; Pollak et al., 2010; Belzung & Lemoine, 2011). In neuropsychiatric research a major focus is placed on construct validity as a key determinant for successful drug discovery, mandating the disease model to be based upon known genetic and/or environmental risk factors — which allows for a recapitulation of the etiological principles involved (Nestler & Hyman, 2010; Fernando & Robbins, 2011; Pratt et al., 2012). Face validity, referring to the analogy between symptoms/features presented in patients and experimental animals can be achieved to varying degrees for animal models of neuropsychiatric disorders, depending on the possibility to reproduce human behavioral features in laboratory animals, as outlined above. Predictive validity – comparable response to treatment of the observed animal phenotype and the human symptomatology – may be considered as less informative in some instances, given the known therapeutic limitations of currently available drug treatments for major psychiatric conditions, including schizophrenia and depression. With this background, neurodevelopmental models are gaining major attention as the knowledge about the relevance of pre- and perinatal environmental insults as major risk factors for the mood and psychotic disorders is increasing (Ansorge et al., 2007; Brown, 2011). Stress-based models, including early maternal separation (Vetulani, 2013), social isolation (Fone & Porkess, 2008) and toxicological approaches such as gestational exposure to methyl-azoxymethanol (Lodge & Grace, 2009), have been most useful in depression and schizophrenia research (Maniam & Morris, 2010; Baek et al., 2011; Marsden et al., 2011; Moller et al., 2013).

Given the relevance of gestational infections as a risk factor for the development of severe neuropsychiatric illnesses (Table 1), several different approaches for the modeling of MIA in laboratory animals have been developed. The currently mostly employed experimental strategies are either based upon i) the use of live viruses, or ii) the administration of immunogenic substances mimicking bacterial or viral infections in the host organism.

The direct application of live viruses constituted the first animal models of gestational infection. Here, the aim was to most closely mimic the epidemiological observations after the influenza epidemic of 1957 (Mednick et al., 1988; Mednick et al., 1994), by the use of live influenza virus (H1N1) (Fatemi et al., 1999; Fatemi et al., 2002a, 2002b). Subsequently, several seminal findings consolidating the link between prenatal infection and brain and behavioral derangements later in life, have been obtained using this approach (see for review: Meyer & Feldon, 2010; Meyer et al., 2009a). While the influenza model of MIA is unarguably closest to the human situation, it also encompasses certain limitations inherent to the use of live pathogens in experimental animals. Importantly, laboratory manipulations involving the handling of infectious agents require the establishment and execution of preventive safety measures in order to minimize personal risks for the experimenters involved. These considerations are unnecessary in the models of viral and bacterial infection relying on the administration of immunogenic substances to the pregnant female, which induce the activation of infection-associated intracellular pathways through binding to TLRs. The two most commonly used approaches are based upon the application of LPS and Poly(I:C):LPS, a gram-negative bacterial cell wall component which mimics bacterial infections binding to TLR4

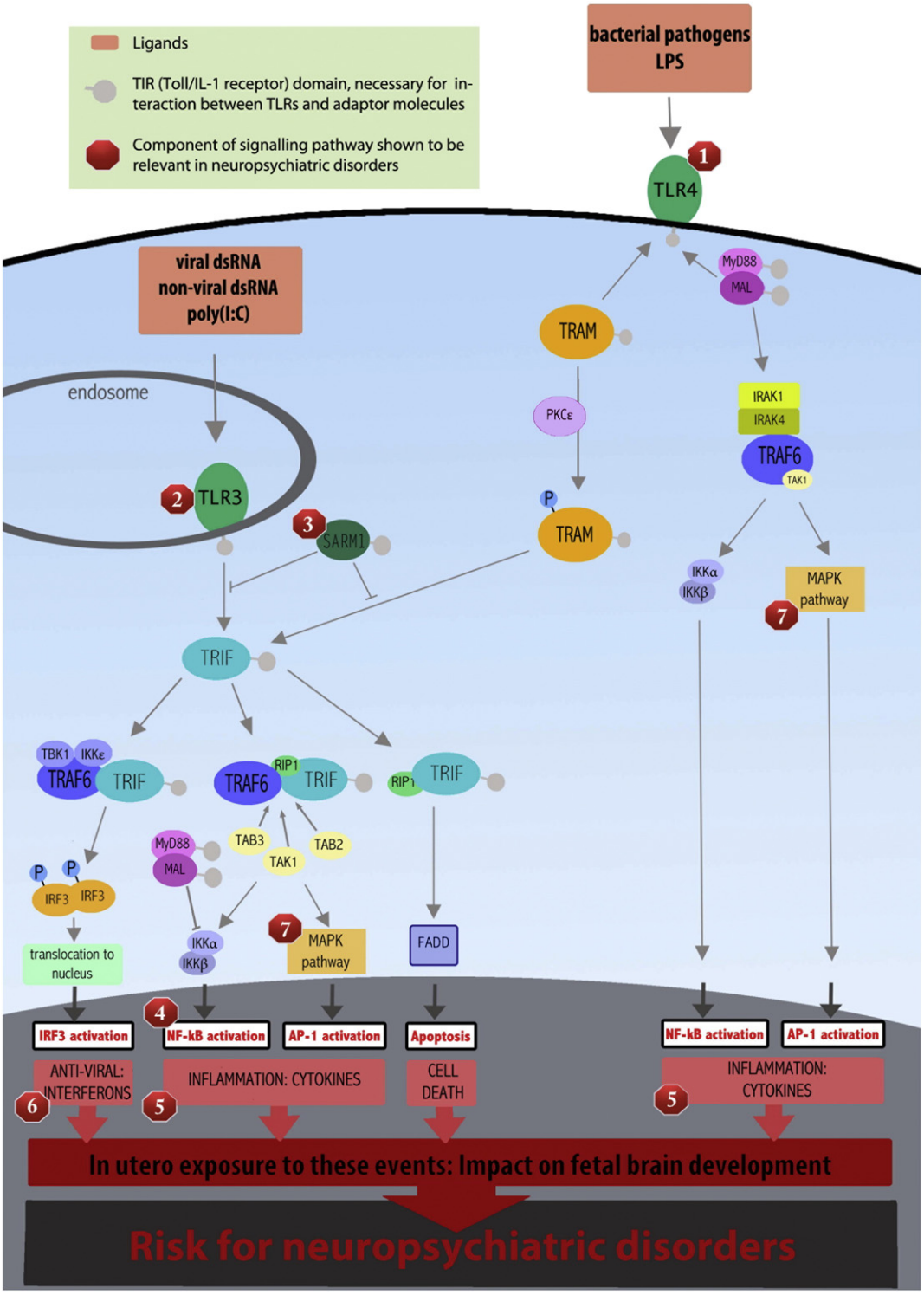

Fig. 2. Involvement of the TLR3 and TLR4 signaling pathways in neuropsychiatric disorders. Several components and processes of the Toll-like receptor (TLR) 3 and TLR4 pathways have been implicated in the etiology of neuropsychiatric diseases as illustrated by selected reports from literature: 1,2 — TLR (Muller et al., 2012; Hoyo-Becerra et al., 2013; Keri et al., 2014; Lin et al., 2014; Pandey et al., 2014); 3 — SARM1 (Lin & Hsueh, 2014; Lin et al., 2014); 4 — NF-kB (Koo et al., 2010; Keri et al., 2014); 5 — proinflammatory cytokines (Dunn et al., 2005; Dowlati et al., 2010; Hannestad et al., 2011; Hiles et al., 2012a, 2012b; Valkanova et al., 2013); 6 — DRIIs (Schlaak et al., 2012; Hoyo-Becerra et al., 2013); 7 — MAPK (Wefers et al., 2012; Mitic et al., 2014; Reus et al., 2014). *Abbreviations*: AP-1 (=activator protein 1), DRIIs (=depression-related interferon-induced genes), FADD (=Fas-associated protein with death domain), IKKs (=inhibitors of NF-kB kinase), IRAKs (=interleukin-1 receptor-associated kinase) 1 and 4, IRF3 (=interferon regulatory factor 3), MAL (=MyD88 adaptor-like), MAPK (=mitogen-activated protein kinase), MyD88 (=myeloid differentiation primary response gene 88), NF-kB (=nuclear factor kappa-light-chain-enhancer of activated B cells), PKCε (=protein kinase C epsilon), SARM1 (=sterile alpha and TIR motif containing 1), TAK1 (=transforming growth factor beta activated kinase-1), TAB (=TAK binding protein) 1 and 3, TLR (Toll-like receptor) 3 and 4; TRAF3 (=TNF receptor-associated factor 3), TRAF6/RIP1 (=TNF receptor-associated factor 6/receptor interacting protein 1), TRAM (=TRIF-related adaptor molecule), TRIF (=TIR-domain-containing adapter-inducing interferon-β).

(Hao et al., 2010; Elovitz et al., 2011), while Poly(I:C) is a synthetically produced dsRNA analog binding to TLR3. DsRNAs are exclusively produced in the context of viral infection and constitute potent activators of the mammalian immune system (Matsumoto & Seya, 2008), eliciting a plethora of intracellular signaling pathways including activation of the IkappaB kinase, extracellular signal-regulated kinase, and c-Jun N-terminal kinase, among others (Park et al., 2006). Additional relevance for both approaches (TLR3- and TLR4-dependent) MIA animal models is conferred by independent observations linking individual molecular elements of the signaling cascades elicited by TLR3 and TLR4 activation to the pathophysiology of neuropsychiatric disorders (Fig. 2). The focus of the present review is specifically on the significance of the Poly(I:C) MIA model in preclinical research on mood and psychotic disorders and its applicability for psychiatric drug validation and discovery.

In light of the epidemiological evidence (Table 1), the Poly(I:C) MIA model presents with a high degree of construct validity and has been repeatedly demonstrated to induce behavioral features related to schizophrenia, autism and depression in adult offspring (face validity). Moreover, structural and functional aberrations in particular brain regions in adult offspring after Poly(I:C)-assisted MIA overlap with known pathophysiological features of mood and psychotic disorders (Fig. 3). To date, phenotypes related to schizophrenia have been most intensively investigated in mice and rats. Specifically, deficits in prepulse inhibition, modulated sensorimotor gating, and decreased latent inhibition – related to the attentional control of selective associative learning and working memory – have been repeatedly confirmed in different laboratories as extensively reviewed elsewhere (Meyer et al., 2009a; Meyer & Feldon, 2010, 2012) (Meyer, 2014b). Lately, evidence for anhedonic deficits – a central manifestation in depressive disorders and a prominent negative symptom of schizophrenia – after prenatal immune challenge by Poly(I:C) is emerging in rats and mice (Khan et al., 2014; Missault et al., 2014). Interestingly, enhanced behavioral despair, as assessed by tests related to depression-like phenotypes in rodents, has been so far only documented in mouse Poly(I:C) offspring (Chen et al., 2011; Khan et al., 2014). Several of these behavioral deficits, together with related deficiencies in brain structure and function, have been found to be reversible by schizophrenia-specific pharmacotherapy (Table 2), suggesting a good predictive validity of the Poly(I:C) MIA model. However, the relevance of the concept of predictive validity for the development of novel experimental animal models and for drug discovery for mood and psychotic disorders has been challenged (Nestler & Hyman, 2010; Fernando & Robbins, 2011; Pratt et al., 2012) based on the fact that "traditional" screens may preferentially detect compounds with "traditional" modes of action.

Together with the epidemiological evidence, results obtained in animal models indicate an involvement of gestational infection in the development of several neuropsychiatric disorders, the underlying molecular pathophysiological principles of which remain to be fully elucidated. Thus, it is reasonable to think of Poly(I:C) and other forms of MIA in animals as models of particular neurobehavioral phenotypes (Fernando & Robbins, 2011) rather than models for specific diseases. Furthermore, just as genes do not encode for psychopathologies (Tan et al., 2008) environmental disturbances (such as prenatal infection) alone do not lead to mental illness. Rather, they can be seen as events associated with an enhanced frequency of alterations in brain morphology and function underlying particular behavioral manifestations, which have been statistically linked to various sets of conditions summarized in the terminology used to denote apparently distinct mental disorders.

All things considered, the successful application of MIA animal models in neuropsychiatric research, specifically in drug discovery, will depend on the combined evaluation of a gamut of phenotypic presentations (endophenotypes) from the molecular to the cellular and systemic (behavioral) levels.

3. The polyinosinic:polycytidylic acid model in comparison to other experimental paradigms of maternal immune activation

As is the case for every model, each MIA paradigm possesses specific advantages and disadvantages, and the suitability for the specific research question to be addressed – from basic neuroscience to the development of novel drug targets – needs to be evaluated individually.

An important advantage of Poly(I:C)-assisted MIA over live pathogens is that Poly(I:C)-induced "sickness-like behavior", characterized by a plethora of endocrine, autonomic and behavioral symptoms induced by proinflammatory cytokines following immune activation, is restricted to a maximum period of 24–48 h (Cunningham et al.,

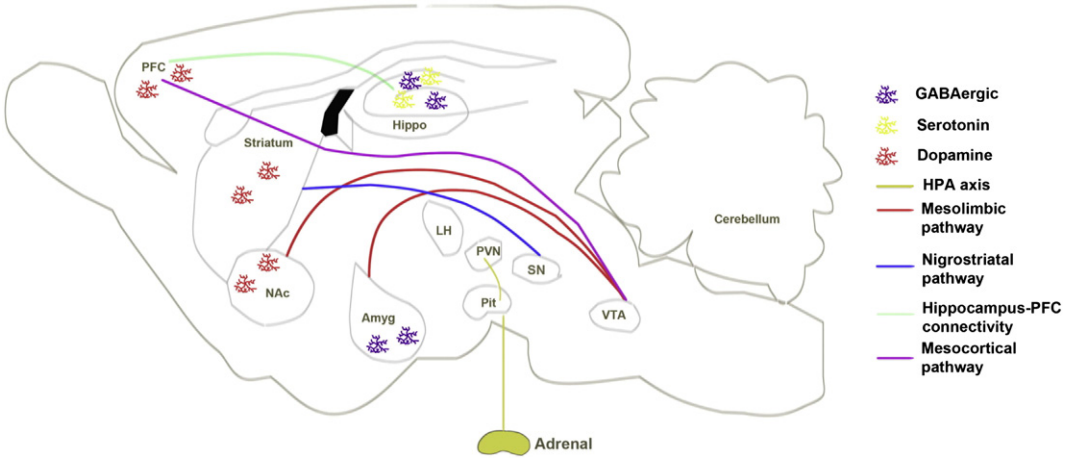

Fig. 3. Structure and function of brain regions impacted by Poly(I:C)-assisted MIA. Abnormalities in the HPA axis commonly associated with depression-like behavior in offspring after Poly(I:C) MIA have been documented (Babri et al., 2013). Alterations in the mesolimbic pathway, projecting from the VTA to the NAc and the Amyg, related to schizophrenia, have been identified in Poly(I:C) MIA offspring (Zuckerman et al., 2003). Prenatal Poly(I:C) is reported to compromise the function of the SN and striatum (Deleidi et al., 2010). Striatal dopamine level reductions reported in Poly(I:C) MIA offspring (Ozawa et al., 2006) are sensitive to antipsychotic treatment (Zuckerman et al., 2003). Alterations to proper cortical functioning in adult offspring from Poly(I:C) MIA and neural synchrony disturbances between the Hipp and PFC, associated with schizophrenia, have been identified in the Poly(I:C) MIA animal model (Zhang et al., 2012; Dickerson & Bilkey, 2013). Compromised levels of dopamine (Bitanihirwe et al., 2010), and serotonin (Winter et al., 2009) are reported in the NAc, Hipp, and PFC and changes in levels of GABA are reported in the Hipp and Amyg (Nyffeler et al., 2006b) in offspring of Poly(I:C) MIA. Structural abnormalities are noted in the Hipp, the striatum, the PFC and lateral ventricles (Piontkewitz et al., 2012). *Abbreviations*: HPA: hypothalamic pituitary adrenal, VTA: ventral tegmental area, NAc: nucleus accumbens, Amyg: amygdala, SN: substantia nigra, Hipp: hippocampus, PFC: prefrontal cortex, GABA: γ-aminobutyric acid, Poly(I:C): polyinosinic:polycytidylic acid, MIA: maternal immune activation.

Table 2
Summary of studies using the Poly(I:C) maternal immune activation (MIA) models to investigate neurobiological mechanisms related to pharmacotherapy of psychotic disorders.

Disease modeled	Reference	Drug	Class of drug	Effects investigated	Results
Schizophrenia	Zuckerman et al., 2003	Haloperidol, clozapine	Typical and atypical antipsychotics	Impaired latent inhibition in adult offspring prenatally exposed to MIA	Haloperidol and clozapine reduced latent inhibition deficits in mice exposed to Poly(I:C)-induced MIA
Schizophrenia	Ozawa et al., 2006	Haloperidol, clozapine	Typical and atypical antipsychotics	Impaired cognitive performance	Chronic administration of clozapine improved cognitive performance in mice exposed to Poly(I:C)-induced MIA
Schizophrenia	Meyer et al., 2010	Clozapine	Atypical antipsychotic	Impairment in working memory and reduction in hippocampal neurogenesis	Chronic administration of clozapine reversed impairments in working memory of mice exposed to Poly(I:C)-induced MIA, no rescue of hippocampal neurogenesis
Schizophrenia	Piontkewitz et al., 2009	Clozapine	Atypical antipsychotic	Structural pathologies including enlarged lateral ventricles and reduced hippocampal volumes, as well as behavioral abnormalities relevant to schizophrenia	Administration of clozapine during peri-adolescence prevented emergence of behavioral abnormalities and structural brain alterations in adulthood in mice exposed to Poly(I:C)-induced MIA
Schizophrenia	Roenker et al., 2011	Risperidone, paliperidone	Atypical antipsychotics	Elevation of basal extracellular glutamate levels in cortex	Chronic administration of risperidone and paliperidone normalized levels of extracellular glutamate in the cortex of mice exposed to Poly(I:C)-induced MIA
Schizophrenia	Piontkewitz et al., 2011	Risperidone	Atypical antipsychotic	Structural (enlarged lateral ventricles, reduced hippocampal volumes) and behavioral abnormalities relevant to schizophrenia	Peri-adolescent risperidone prevented behavioral abnormalities and structural brain alterations in adulthood in mice exposed to Poly(I:C)-induced MIA
Schizophrenia	Piontkewitz et al., 2012	Risperidone	Atypical antipsychotic	Impaired neurogenesis, disturbed micro-vascularization and loss of parvalbumin-expressing hippocampal interneurons	Peri-adolescent risperidone prevented most neuropathological changes in mice exposed to Poly(I:C)-induced MIA
Schizophrenia	Dickerson & Bilkey, 2013	Clozapine	Atypical antipsychotic	Disrupted synchronization of hippocampal and medial prefrontal neural networks	Acute administration of clozapine rescued impairment in long-range neural synchrony in adult mice exposed to Poly(I:C)-induced MIA

2007). Compared with the potentially longer-lasting and less controllable time course of infection with live pathogens, the relatively short-lived and defined immune response elicited by Poly(I:C) allows for the precise timing of the immunogenic impact, hence allowing for specific associations of immune activation with defined stages of embryonic brain development (Theiler, 1972; Rutledge, 1997). Indeed, several studies using the Poly(I:C) MIA model have significantly contributed to the elucidation of the distinct time periods during prenatal development which seem to constitute specific windows of vulnerability to environmental insult. Hence, specific neurobehavioral alterations in adulthood are associated with the exposure to MIA at particular stages of fetal development, as elegantly demonstrated in a series of studies employing Poly(I:C)-assisted MIA (Meyer, Feldon, Schedlowski, & Yee, 2006; Meyer et al., 2006a, 2006b; Meyer et al., 2007). For example, MIA at gestational day 9 and gestational day 12.5 have resulted in schizophrenia-like behavior in adult offspring, such as impaired sensorimotor gating, decreased prepulse inhibition and increased startle sensitivity (Meyer et al., 2005 #78; Meyer et al., 2006a, 2006b). Poly(I:C) administration at gestational day 12.5 has additionally been reported to induce enhanced anxiety-like behavior (Hsiao et al., 2012) and depression-like behavior in the offspring (Khan et al., 2014). Alternatively, offspring from Poly(I:C) MIA at later gestational time periods, such as gestational day 16 or gestational day 17, demonstrated increased seizure susceptibility, reduced social index scores, thigmotaxis, and cognitive impairment (Ozawa et al., 2006; Pineda et al., 2013), phenotypes related to epileptic and cognitive disorders.

The critical relevance of the particular gestational stage during which maternal immune activation is induced may relate to both maternal and fetal factors. First, the immune response in the maternal system significantly varies during the course of pregnancy (Sargent, 1993; Tinsley et al., 2009; Chatterjee et al., 2011), thus determining the nature and intensity of exposure of the fetus to inflammatory mediators. Second, the vulnerability of the fetal nervous system may depend on the actual developmental period, as indicated by epidemiological evidence reporting an increased likelihood for offspring brain and behavioral aberrations specifically associated with maternal infection during the late first and early second trimester of pregnancy (Mednick et al., 1988; Brown et al., 2004; Atladottir et al., 2010). This observation may relate to the fact that the development of the immune system is only completed during late gestation and the postnatal period (Holsapple et al., 2003).

Considering the pleiotropic effects of cytokines on aspects of neuronal morphology, function and survival (Hinze-Selch et al., 1998; Potter et al., 1999; Marx et al., 2001; Gilmore et al., 2005; Deverman & Patterson, 2009) the neurodevelopmental and neurobehavioral outcome after MIA may directly relate to the specific cytokine status of the fetal brain at a particular point of development (Meyer et al., 2006a, 2006b; Lajtha, 2008; Meyer et al., 2008b). Differential permeability of the placenta, an immunologically highly active organ (Zourbas et al., 2001; Bowen et al., 2002; Ostojic et al., 2003), during the course of pregnancy (Dahlgren et al., 2006) has to be considered as an additional variable determining fetal cytokine exposure and related long-term consequences. However, the specific mechanisms underlying the passage of individual cytokines through the maternal–fetal interface at particular gestational stages remain incompletely understood (Jonakait, 2007; Lim & Kobzik, 2009).

Apart from the possibility to stringently control the timing, gestational Poly(I:C) administration also allows for rigorous constraints on the intensity of the immunogenic stimulation and the associated maternal immune response. Correspondingly, seminal experiments have demonstrated a defined dose-dependency of adult behavioral impairments resulting from MIA using the Poly(I:C) model (Meyer et al., 2005; Fortier et al., 2007; Wolff & Bilkey, 2010).

Furthermore, sex-specific effects of MIA have been noted pertaining to differential behavioral outcomes in male and female offspring (Hodyl et al., 2007; Schwendener et al., 2009; Bitanihirwe et al., 2010; Chlodzinska et al., 2011; Enayati et al., 2012; Vorhees et al., 2012; Bronson & Bale, 2014). Dose-dependency, together with the observed offspring sex-effects of MIA may present additional variables to be considered within a complex set of interacting factors defining neurobehavioral outcomes after prenatal infection.

Within the frame-work of the "multiple-hit hypothesis" (Meyer et al., 2008a; Meyer & Feldon, 2010; Brown, 2011; Giovanoli et al., 2013), MIA may constitute one specific environmental insult impinging on the specific genetic make-up of an individual and/or serve as "priming" factor, predisposing an individual – upon confrontation with further challenging stimuli (such as additional stress exposure later in life; Giovanoli et al., 2013) – to the development of mental illness. Concerning *gene* × *environment* interactions as the biological interface for the long-established "nature versus nurture" etiological principle, the Poly(I:C) MIA model has contributed to the elucidation of some of the key players involved in the pathogenesis of schizophrenia (Ozawa et al., 2006; Dickerson & Bilkey, 2013; Van den Eynde et al., 2013). For example, following Poly(I:C)-assisted MIA, mice with mutations in the Disrupted in Schizophrenia 1 gene (DISC1) – originally identified in a case of familial human schizophrenia (Chubb et al., 2008; Jaaro-Peled et al., 2009) – display higher susceptibility to the development of behavioral features associated with schizophrenia (Lipina et al., 2013). These data indicate a potential interplay between proinflammatory cytokines such as interleukin-6 (IL-6) resulting from MIA (Smith et al., 2007) and DISC1 in the pathogenesis of schizophrenia spectrum disorders (Chubb et al., 2008). Additionally, specific epigenetic modifications at the DISC1 gene locus upon prenatal Poly(I:C) exposure have been reported (Connor et al., 2012), adding a further level of complexity to the intricate web of pathomechanisms forming the biological underpinnings of psychiatric disease development. Similarly, an interaction of Poly(I:C) MIA with mutations in the nuclear receptor related protein 1 (NURR1) gene, encoding for a transcription factor controlling dopaminergic development, has been found to underlie the effects on behavioral and neuropathological alterations in the adult offspring (Vuillermot et al., 2012).

Despite its advantages, there are also limitations to the Poly(I:C)-based MIA animal paradigm. Apart from the "traditional", general concerns relating to the usage of rodent systems to model complex neuropsychiatric disorders, which present with alterations of inherently "human" behavioral features, there are also experimental specifics of Poly(I:C)-assisted MIA that need to be taken into consideration for the design and interpretation of individual studies. The major drawback of using immunogenic manipulations based upon Poly(I:C) or LPS, rather than live pathogens, is the – albeit well-characterized – limited set of immune responses elicited (Baldwin, 1996; Cunningham et al., 2007; Chen et al., 2011; Chlodzinska et al., 2011; Paris et al., 2011; Arrode-Bruses & Bruses, 2012; Connor et al., 2012; Diz-Chaves et al., 2012; Babri et al., 2013). Comparatively, stimulating the maternal immune system by administration of a real virus (such as influenza), leads to a much broader activation of not only the innate, but also the acquired immune system, thus more closely resembling the situation following infection during pregnancy in humans (Meyer, 2014a).

4. The polyinosinic:polycytidylic acid maternal immune activation model in the investigation of psychopharmacological treatment approaches

Currently available pharmacological treatment options for both psychotic and mood disorders are still insufficient, with a large percentage of the patient population not satisfactorily responding to the commonly prescribed drug regimens (Maes et al., 1997; Buckley et al., 2001; Conley & Kelly, 2001; Kubera et al., 2001; Gaynes, 2009; El-Hage et al., 2013; Spijker et al., 2013). Even among the designated "responders", complete remission rates remain low (Bisgaard et al., 2007; Buckley et al., 2001; Mouaffak et al., 2006; Schlaepfer et al., 2013) and patient compliance is compromised by the frequent experience of adverse side effects associated with psychopharmacotherapy (Blair & Dauner, 1992; Zimbroff et al., 1997; Bilder et al., 2002; Siegel et al., 2002; Kroeze et al., 2003; Jaaro-Peled et al., 2009; Abbasi et al., 2010). In the search for novel therapeutic strategies, the Poly(I:C) MIA rodent model has become very attractive in recent years due to its well-documented validity, thus far assessed mainly in the context of schizophrenia-like phenotypes in rats and mice (Zuckerman et al., 2003; Ozawa et al., 2006; Romero et al., 2007; Meyer, Knuesel, Nyffeler, & Feldon, 2010; Piontkewitz et al., 2012) and recently beginning to be explored in the context of MDD (Khan et al., 2014). Hence, Poly(I:C)-assisted MIA serves as a naturalistic animal model to further characterize molecular and structural neuronal alterations resulting from the treatment with common psychopharmacological medication.

4.1. Polyinosinic:polycytidylic acid-assisted maternal immune activation for the investigation of established psychopharmacological drugs

Elucidation of the precise neurobiological mechanisms underlying the effect of established psychopharmacological drugs, which – although already in therapeutic use for decades – remain incompletely understood, may aid in the identification of alternative, potentially more specific drug targets and/or strategies to combat undesired side effects. For example, treatment with the atypical antipsychotic risperidone has been found to rescue aberrant hippocampal neurogenesis, parvalbumin expression and vascularization resulting from gestational Poly(I:C) administration in rats (Piontkewitz et al., 2012). Interestingly, sex-specificities in the effects of long-term clozapine or risperidone treatment during adolescence and during adulthood have also been reported (Piontkewitz et al., 2012), which additionally suggests Poly(I:C) MIA as a preclinical model for the investigation of gender-differences in disease susceptibility and drug response in psychiatric disorders.

Further, acute treatment with clozapine, the first atypical antipsychotic drug available, was reported to reverse impaired long-range neural synchrony between the hippocampus and medial prefrontal cortex (mPFC), a particular functional deficit observed in the Poly(I:C) MIA rat model which is associated with the presentation of schizophrenia-like behavior (Dickerson & Bilkey, 2013). The effect of clozapine on the reduced coupling between the mPFC and the hippocampus may contribute to its therapeutic effects in schizophrenia, and the Poly(I:C) MIA model may serve as a tool to investigate the molecular changes underlying the observed functional deficits, potentially leading to the exploration of novel intervention strategies targeting these molecules (Dickerson & Bilkey, 2013). Along these lines, NMDA glutamate receptor hypofunction, which was effectively blocked by low dose treatment with paliperidone or risperidone, has been proposed as an early developmental consequence of prenatal Poly(I:C) exposure. Hence, the Poly(I:C) MIA model may serve as a tool for the identification of early therapeutic interventions directed at the glutamatergic system, which is known to also be involved in the manifestation of positive and negative symptoms in patients suffering from schizophrenia (Roenker et al., 2011). Supporting the role of NMDA receptors in the mechanistic underpinnings of pharmacotherapy, hippocampal slices of offspring from Poly(I:C) MIA show NMDA/glutamatergic receptor activity specifically related to clozapine and not to haloperidol (Wittmann et al., 2005).

In the case of currently used antidepressant drugs, long-term treatment with either the SSRI fluoxetine or the antipsychotic aripiprazole has been shown to completely reverse amphetamine-induced locomotor activation in offspring after Poly(I:C)-based MIA (Richtand et al., 2012). Behavioral effects of antidepressants in this model are especially important considering recently emerging evidence that not only features relevant to the symptomatology of schizophrenia, but also depressive-like behavior is observed in offspring after prenatal immune activation using either Poly(I:C) (Khan et al., 2014) or LPS (Babri et al., 2013; Lin & Wang, 2013).

Thus, in addition to the well-established predictive validity of the Poly(I:C) MIA rodent model for schizophrenia, the power of the paradigm as a tool for drug validation and discovery in depression research is only beginning to be explored. In this fashion, alterations of the glycogen synthase kinase-3 β (GSK-3β) signaling pathway, the target of the classic mood stabilizer lithium that reduces both depression-like and manic-like behaviors in rodents (see for review Jope, 2011), in the

Poly(I:C) MIA mouse model (Willi et al., 2013), lend support to its further applicability in the study of the incompletely understood molecular mechanisms underlying the high treatment efficacy of lithium (Conley & Kelly, 2001; Basselin et al., 2007; Jope, 2011). This approach could potentially lead to the identification of refined drug targets within the relevant signaling pathways. A summary of the studies using the Poly(I:C) MIA rodent model in preclinical research to investigate mechanisms underlying the action of currently prescribed pharmacological treatments can be found in Table 2.

4.2. Polyinosinic:polycytidylic acid-assisted maternal immune activation in the discovery of novel therapeutic strategies

Lately, the Poly(I:C) MIA model is emerging as an extremely potent preclinical research tool in the quest for both symptomatic and preventive treatment approaches aiming to ameliorate or restrict behavioral and neurobiological dysfunctions resulting from gestational infection. In both cases, the Poly(I:C) MIA model is ideally suited for the development, characterization and screening of novel compounds. Symptomatic therapies can be evaluated in the adult offspring without any regard to possible drug interactions or to the effects of other acute manipulations, which may be potentially confounding in other animal models. Here, the experimental induction of the phenotype is carried out in-utero, long before the manifestation and examination of the phenotype to be studied. Accordingly, the concept of a prenatal manipulation that gives rise to the manifestation of psychiatric symptoms in adulthood also represents an advantageous approach by which factors contributing to the progression of the disease, as well as therapeutic strategies aiming at preventing the onset of the disease later in life, can be identified during the individual's adolescent period.

This aspect is particularly relevant in the case of schizophrenia, where it is known that the entire range of behavioral and associated neurobiological alterations marking the full-blown disorder usually emerge during early adulthood, with the adolescent period constituting a "window of vulnerability" determining onset, course and severity of the disease (Meyer et al., 2007; Patterson, 2007; Li et al., 2009; Meyer & Feldon, 2012; Michel et al., 2012; Schimmelmann et al., 2013; Meyer, 2014b). Here, ground-breaking work has been carried out using the Poly(I:C) MIA model investigating both the factors contributing to disease manifestation in adulthood (Meyer et al., 2008a; Vuillermot et al., 2010; Giovanoli et al., 2013), as well as the beneficial effects of early preventive pharmacological interventions (Piontkewitz et al., 2009; Meyer, Spoerri, Yee, Schwarz, & Feldon, 2010; Piontkewitz et al., 2012).

Most of these studies focus on schizophrenia, which is commonly classified as a "neurodevelopmental disorder" (Piontkewitz et al., 2012; Zhang et al., 2012), and in which a clinically latent period during childhood (pediatric schizophrenia is very rare; Brent et al., 2013) is followed by a clinically validated prodromal stage during which patients present with vague and unspecific symptoms (Brent et al., 2013). Accordingly, early therapeutic interventions during the peri-adolescent period may exploit a window of opportunity for preventing disease progression and consequently associated negative impacts on patients' personal, social and professional lives, as well as augmented risks for the development of additional psychiatric diseases. Interestingly, chronic treatment during peri-adolescence with not only antipsychotic, but also antidepressant medication has been reported to effectively prevent schizophrenia-like behavior after prenatal exposure to Poly(I:C) (Meyer et al., 2010), paralleling results of a human study (Cornblatt et al., 2007). However, although sub-threshold symptoms during adolescence are similarly known to confer heightened risks of later depression and suicidal behaviors (Fergusson et al., 2005), the potential effects of preventive treatment on the depression-like phenotype in adulthood observed after Poly(I:C) MIA (Khan et al., 2014) have not yet been investigated.

In the light of evidence indicating that the duration of untreated psychiatric manifestations is not only associated to the extent of psychosocial damage suffered (Ho et al., 2000), but also correlates to the subsequent responsiveness to pharmacological treatment (Ho et al., 2003; Marshall et al., 2005; Perkins et al., 2005; Melle et al., 2008; Farooq et al., 2009), the possibility to prevent disease outbreak by early pharmacological intervention seems very appealing. However, there are important limitations and concerns related to early preventive drug treatment (see for review Francey et al., 2010). Importantly, the ability to properly anticipate – at early stages of (disease) development – individuals who are at high risk for the development of psychiatric disorders entirely depends on the validity and the predictive power of the criteria applied (Francey et al., 2010). With a current transition rate of less than 20% for psychotic disorders (Yung et al., 2008; Ruhrmann et al., 2010), the number of subjects who would be receiving unneeded psychopharmacological treatment ("false-positives") is high and raises important ethical concerns (Block, 2006), especially considering that the corresponding experimental research is still in its infancy. Here the Poly(I:C)-assisted MIA in rodents constitutes a highly relevant tool for the budding exploration, in a preclinical research setting, of both beneficial as well as adverse effects associated with early preventive drug treatment. Indeed, using the Poly(I:C) MIA mouse model it was found that chronic psychopharmacotherapy during the peri-adolescent period in "healthy" control animals (corresponding to false-positive subjects in the human population) resulted in an enhanced risk for behavioral alterations later in life (Meyer et al., 2010).

These data highlight the necessity for further characterization at the molecular, cellular and behavioral levels of the full spectrum of – so far incompletely understood – intermediate and long-term consequences resulting from early preventive drug treatment regimes. The Poly(I:C) MIA model is proposed as an ideal tool for addressing these questions as differential effects of pharmacotherapy can be evaluated in "true" high-risk (i.e. offspring having undergone prenatal Poly(I:C) exposure) and "false-positive" (i.e. offspring having undergone vehicle control exposure) individuals in parallel. Moreover, Poly(I:C)-assisted MIA is a highly suitable paradigm in the search for novel preventive therapeutic strategies as it recapitulates the neurodevelopment aspect related to the etiology of psychiatric conditions, including psychotic and mood disorders (Meyer et al., 2005; Meyer et al., 2010). Indeed, several studies taking advantage of the Poly(I:C) MIA model to identify additional preventive pharmacological approaches have recently emerged. One example is the use of antibiotic therapies in order to attenuate the progression of behavioral as well as cellular and molecular deficits related to neuropsychiatric disease development (Mattei et al., 2014; Zhu et al., 2014).

Similarly, the successful application of the Poly(I:C) MIA paradigm in the quest to identify new symptomatic treatment options for neuropsychiatric conditions will require the integration of the effects of candidate molecules on Poly(I:C) MIA-induced alterations — from the single molecule via the neural circuitry to the behavioral level (see Fig. 3). Examples for such approaches include a recent rat μPET study which in a longitudinal assessment of dynamic protein expression changes, reported age- and region-specific impairment of the endocannabinoid system in Poly(I:C) offspring (Verdurand et al., 2014). This study supports the use of Poly(I:C) MIA in the targeted and detailed analysis of the pathogenic and therapeutic relevance of molecules associated with the endocannabinoid signaling pathway, which has been previously related to several neuropsychiatric conditions, including schizophrenia and depression (see for review Marco et al., 2011). In the case of ASD, for which the Poly(I:C) MIA rodent model has been also repeatedly validated (Schwartzer et al., 2013; Missault et al., 2014), recent results using this model suggest hyperpurinergia to be fundamental to the observed deficiencies, as well as being highly treatable — thereby potentially refining therapeutic strategies for ASD (Naviaux et al., 2014; Naviaux et al., 2013). Intriguingly, the purinergic signaling system is also implicated in the pathogenesis of both MDD (Cao et al., 2013) and schizophrenia (Burnstock et al., 2011; Wonodi et al., 2011), highlighting the Poly(I:C) MIA model as a valuable model system for the investigation

of potential structural and functional neuropathological commonalities between these three intricate neuropsychiatric disorder complexes.

Hence, these diseases may not only present with overlapping clinical and therapeutic features, but may also share some of the underlying etiological bases. In this vein, accumulating evidence suggests a vital role of epigenetic modifications, including dynamic posttranslational modifications to histones, in the pathophysiology of these mental illnesses (Darnaudéry & Maccari, 2008; Mueller & Bale, 2008; Brown, 2011; Uchida et al., 2011; Connor et al., 2012; Tang et al., 2013) and therapeutic concepts based upon these observations are under development (Feder et al., 2009; Masi & Brovedani, 2011; Anderson et al., 2013). Indeed, global changes of histone acetylation and methylation statuses as well as promoter-specific alterations have been identified in the brains of offspring after prenatal exposure to Poly(I:C) (Tang et al., 2013). In contrast, another recent report concludes that maternal immune stimulation by Poly(I:C) may not significantly alter epigenetic regulation of gene expression in the cerebral cortex of adult offspring (Connor et al., 2012).

These conflicting data highlight the relevance of future research in order to clarify the contribution of epigenetic mechanisms to the observed behavioral and molecular alterations associated with neuropsychiatric disorders.

5. Conclusions and future perspectives

The currently most widely accepted concept – supported by evidence from epidemiological, clinical as well as basic neuropsychiatric research – proposes a convoluted web of multiple interacting factors to constitute the biological underpinnings of complex neuropsychiatric disorders. Here, the ancient perception of "nature versus nurture" is reflected in *gene × environment* interactions with various different environmental factors additionally interacting with each other. One environmental factor repeatedly emerging as critical for the etiology of several major mental disorders, including schizophrenia, autism and depression, is gestational infection. Increasing the understanding – at the molecular, cellular and systemic levels – of the pathomechanisms involved in these burdensome diseases is a prerequisite for improving the still unsatisfactory pharmacotherapeutic options available today. Within this framework, we propose the rodent model of maternal immune activation, based upon the stimulation of the pregnant dam with Poly(I:C), as a relevant and suitable tool for preclinical drug research, as summarized in the following points previously outlined in this review:

1) Feasibility and reproducibility of the experimental handling
2) Control over specific stimulation intensity and precise timing
3) Sensitivity to treatment with available psychopharmacological agents
4) Exemplarily demonstrated interaction with determined genetic factors
5) Evidence for interaction with distinct environmental impacts
6) Modeling of disease progression as opposed to single-point acute manipulation(s)
7) Development and testing of novel preventive and symptomatic therapeutic strategies.

Nevertheless, regarding the conceptual comprehension of the etiology of the mental illnesses outlined above, and inherent to the use of animal models in neuropsychiatric research, several important constraints need to be taken into account:

1) Some symptoms of human (psychiatric) disorders currently are – and will most likely remain – impossible to model in experimental animals.
2) No single animal model can reproduce the entire spectrum of behavioral and neuropathological features characteristic of a psychiatric entity in the human population.
3) Current criteria defining the validity of animal models will need to be refined as our understanding of the neurobiological bases underlying the particular diseases increases, possibly leading to retrospective re-evaluation of existing paradigms.
4) Maternal immune activation, based upon Poly(I:C), or any other gestational infection/immune challenge procedure, has to be considered as a model for one, developmentally-based, environmental challenge condition, rather than as a complete recapitulation of an entire neuropsychiatric phenotype.
5) Maternal immune activation most likely constitutes a shared pathogenic feature involved in the etiology of several severe mental illnesses, rather than a model for an individual disease.
6) The complex web of vulnerability factors interacting at the genetic, epigenetic and environmental levels contributing to the pathogenesis of mental illness, remains incompletely understood to date.
7) Our understanding of the longitudinal aspect of disease progression of psychiatric disorders with a proposed background of neurodevelopmental disturbances, as well as relevance and consequences of early preventive interventions, is currently still limited.

Taken together, the rodent Poly(I:C) maternal immune activation protocol is suggested as a valuable experimental approach on the path to the development of new therapeutic strategies aiming at combating highly complex and debilitating human psychiatric diseases. The fruitful application of this model in neuropsychiatric drug discovery, however, will critically depend on the implementation of an analytical strategy which combines behavioral assessments with the evaluation of various endophenotypes in order to improve the chances for successful translation of newly discovered treatment approaches to clinical applications.

Declaration of interest

The authors declare no conflict of interest. The present manuscript has not been previously published and is not under consideration for publication elsewhere.

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