Maternal Immune Activation by Poly I:C as a preclinical Model for Neurodevelopmental Disorders: A focus on Autism and Schizophrenia

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Abstract
Maternal immune activation (MIA) in response to a viral infection during early and mid-gestation has been epidemically linked to a higher risk for the child to develop autism or schizophrenia-related symptoms. This has led to the establishment of the pathogen-free poly I:C induced MIA animal model for neurodevelopmental disorders with relatively high construct and face validity. Depending on the experimental variables, particularly the timing of poly I:C administration, different behavioural and molecular phenotypes have been described that relate to specific symptoms of neurodevelopmental disorders such as autism spectrum disorder and/or schizophrenia. We here review and summarize epidemiological evidence for the effects of maternal infection and immune activation, as well as major findings in different poly I:C MIA models with a focus on poly I:C exposure timing, behavioural and molecular changes in the offspring, and characteristics of the model that relate it to autism spectrum disorder and schizophrenia.

Keywords
Maternal immune activation, viral infection during pregnancy, prenatal brain development, environmental impact on brain development, schizophrenia, autism spectrum disorder, animal model

Highlights

- A review of epidemiological evidence highlights important considerations for poly I:C MIA models
- Maternal immune activation by poly I:C is a model for neurodevelopmental disorders
- This model has a high construct, face, and predictive validity
- Poly I:C offspring show core symptoms of autism and schizophrenia, confirming epidemiological evidence linking those disorders with maternal infection
- Different gestational exposures lead to different offspring outcomes
- Cytokine signaling is heavily involved in neurodevelopment and likely mediates poly I:C's effects

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Table of Contents

1. Introduction

Prenatal brain development is an elaborate process during which any external environmental influence can be severely detrimental to the individual. This is exemplified in a variety of high-profile effects caused by fetal exposure to alcohol, nicotine, psychoactive drugs or maternal diet alterations during pregnancy (Barker, 1995; Ross et al., 2015). The human brain is particularly susceptible during this period as it undergoes an enormous degree of prenatal development, with vital processes such as neurogenesis, neural migration, and basic connections being, in large part, completed by birth (translatingtime.org; Workman et al., 2013). It is therefore unsurprising that even slight environmental impacts during these extensive developmental processes can lead to long-lasting structural and functional alterations in the offspring. Maternal infection during pregnancy is one such environmental insult. The harmful effects of maternal infection during pregnancy are epitomized by the recent Zika outbreak and its association with microcephaly in offspring born to infected mothers (de Oliveira and da Costa Vasconcelos, 2016; Klase et al., 2016). While the Zika findings gained a lot of recent attention, the hypothesis that maternal infection negatively influences offspring brain development has been heavily investigated in the last two decades.

Interest in maternal infection was ignited by epidemiological studies linking seasonal births or influenza epidemics with an increased incidence of psychiatric disorders (reviewed by Brown and Derkits, 2010). Follow up studies unraveled the relationship between a wide variety of different infections occurring during early pregnancy and the risk of psychiatric disorders in the offspring - particularly those with a neurodevelopmental component. Some of these studies went as far as to link specific maternal serological immune markers with the risk increase (Abdallah et al., 2013; Brown et al., 2004b; Goines et al., 2011). Disorders most commonly associated with maternal infection are autism spectrum disorder (ASD) and schizophrenia (SCZ), although direct and indirect associations with other disorders do exist (Knuesel et al., 2014).

Given that the majority of ASD and SCZ cases are idiopathic and that only a small subset of known cases can be attributed to monogenic causes (Henriksen et al., 2017; Voineagu et al., 2011), the association of a common environmental factor like maternal infection has tremendous implications for understanding the etiology of these complex disorders. In addition, environmental factors are particularly important to consider in polygenic disorders such as ASD and SCZ where they can

trigger genetic predispositions in otherwise typically developing individuals (Insel, 2010; Varghese et al., 2017).

Broadly, effects of maternal infection can be attributed to two main culprits: The infectious agent and the maternal immune response that develops against it. While pathogen-specific effects exist such as in the case of the Zika virus, evidence from epidemiological studies seems to implicate the maternal immune response rather than specific infectious agents in the increased offspring risk of developing ASD and SCZ (Brown and Derkits, 2010). Associations of different infections in pregnant mothers with the same disorder risk for the offspring indicate a common underlying mechanism where the maternal immune response is the most logical candidate. Additionally, associations of specific immune markers common to both viral and bacterial infections with the degree of risk adds further evidence to this hypothesis (Abdallah et al., 2013; Brown et al., 2004b; Goines et al., 2011). Therefore, the maternal immune response emerged as the likely culprit through which different types of infection can increase the risk of ASD and SCZ, although this does not eliminate the significance of pathogen-specific effects as seen with Zika. This evidence served as the basis for maternal immune activation (MIA) preclinical models, which set out to decipher the effects of the maternal immune response on offspring brain development and the resulting functional and behavioural changes in the offspring. MIA models utilize pathogen-associated molecular markers to elicit an acute pathogen-free immune response during gestation. Commonly, the bacterial cell-wall component lipopolysaccharide (LPS) or the synthetic double stranded RNA (dsRNA) analogue polyinosinic polycytidylic acid (poly I:C) are used to elicit bacterial or viral innate immune responses, respectively.

Over the past 15 years, poly I:C models have been frequently used as a preclinical model to study an environmental cause of ASD and SCZ-like symptoms in rodents (Boksa, 2010; Knuesel et al., 2014; Meyer et al., 2011; Reisinger et al., 2015; Scola and Duong, 2017; Solek et al., 2018) and to a lesser extent in non-human primates (Bauman et al., 2014; Machado et al., 2015; Rose et al., 2017; Weir et al., 2015). This viral MIA model has shown substantial face, construct, and predictive validity, as demonstrated in a large body of literature. In this review, we first revisit some epidemiological evidence that provides the basis for the poly I:C model, focusing on viral infections and their associations with psychiatric disorders in the offspring. Next, we introduce poly I:C and some methodological considerations that are pertinent to the field such as translating developmental timelines across species. We then group and summarize results from poly I:C MIA

studies, focusing on MIA timings that have commonly been investigated and discussing results from each MIA timing in context of the aforementioned methodological variables. Finally, we will provide some insight into the model's findings relating to aspects of ASD and SCZ such as symptomatology and sexual dimorphism.

2. Background and Experimental Considerations

2.1. Infections and Neurodevelopmental Disorders – Epidemiological Evidence

Epidemiological studies overview

Initial epidemiological studies that were interested in the effects of infection exposure during pregnancy were published with a focus on the 1957 Influenza pandemic (please see **supplementary Table S1** for a list of epidemiological evidence). In the period between 2000 and 2010, studies were also beginning to focus on other exposures such as general occurrence of infection (Sørensen et al., 2009), infections affecting different organ systems (Babulas et al., 2006; Byrne et al., 2007) or specific exposures to toxoplasma gondii (Brown et al., 2005), Cytomegalo virus (CMV; Blomström et al., 2012), Herpes Simplex Viruses (HSV) 1 & 2 (Buka et al., 2001) and Rubella (Brown et al., 2001). Additionally, these new studies took a new approach by measuring exposure through the presence of pathogen-specific antibodies, instead of simply investigating hospital records or maternally-reported data (distinguished in our table as presence vs. occurrence). Typically, these were case-control studies that identify patients based on the International Classification of Diseases (ICD) or Diagnostic and Statistical Manual of Mental Disorders (DSM) and retrospectively examine exposure data. With the rise of the MIA hypothesis, exposure measures became more specific to maternal inflammatory markers with the most common ones measured being Interleukin-6 (Abdallah et al., 2013; Allswede et al., 2016; Brown et al., 2004b; Goines et al., 2011; Goldstein et al., 2014; Jones et al., 2017; Mac Giollabhui et al., 2019), C-reactive protein (Brown et al., 2014; Canetta et al., 2014; Koks et al., 2016; Zerbo et al., 2016) and Tumor Necrosis Factor (Abdallah et al., 2013; Allswede et al., 2016; Brown et al., 2004b; Goldstein et al., 2014; Jones et al., 2017; Mac Giollabhui et al., 2019).

In general, many different exposures were associated with SCZ/ASD, as can be seen in **supplementary Table S1**, supporting the MIA hypothesis that immune activation rather than specific pathogens are involved in disrupting neurodevelopment. The association of maternal infection and MIA with SCZ was established by the early waves of epidemiological studies, and evidence for the associations with ASD only recently began to accumulate. In addition, some studies have associated maternal exposures with specific SCZ or ASD-related behavioural outcomes, rather than simply a diagnosis of the disorders (Brown et al., 2009; Koks et al., 2016; Mazina et al., 2015; Slawinski et al., 2018).

Timing, Type and extent of infection, interaction with other risk factors

Epidemiological findings support a bigger neurodevelopmental risk for maternal infection exposures in the first and second trimester, although there has been more evidence for SCZ compared to ASD and more evidence highlighting the risk of infection in the second trimester (Atladóttir et al., 2010; Barr et al., 1990; Brown et al., 2004b; Hornig et al., 2018; Izumoto et al., 1999; Limosin et al., 2003; Mednick et al., 1988; Sham et al., 1992; Suvisaari et al., 1999; Takei et al., 1994, p. 199, 1996) as opposed to the first (Atladóttir et al., 2010; Brown et al., 2004; Morgan et al., 1997; Sørensen et al., 2009). Studies that report timingspecific risks are marked in **Table S1** by ★. In addition, more severe infection has been shown to lead to bigger risk, and this is typically measured as the number of hospital visits, the number of infections or number and extent of febrile episodes (Atladóttir et al., 2012; Fang et al., 2015; Hornig et al., 2018; Zerbo et al., 2015; relevant findings marked by ♣ in **Table S1**). On a similar note, the severity of molecular changes associated with infection also seems to play a role in determining the risk for development of SCZ or ASD in the offspring, and this has typically been measured as pathogen-specific antibodies (Brown et al., 2005; Mortensen et al., 2007; Spann et al., 2017) and levels of cytokines or CRP (Allswede et al., 2016; Brown et al., 2014; Koks et al., 2016). In the study by Brown et al. (2014), there was a 43% increase in risk when comparing the group with upper quartile CRP levels against the group with the lower quartile CRP levels. Beyond the infection itself, interaction with other risk factors, genetic or environmental, can have a synergistic effect with maternal infection (relevant findings marked in **Table S1** with a ∆). In context of gene mutations or single nucleotide polymorphisms (SNPs), it seems that this effect is unique to certain genes and certain SNPs within those genes, with examples given in the study by Demontis et al. (2011) who focused on genes associated with NMDA receptors. Alternatively, exposure to maternal infection has been reported to increase the

risk of SCZ only in cases with family history of psychiatric disorders (Blomström et al., 2012; Clarke et al., 2009) or experiences of peripubertal trauma (Debost et al., 2017).

Limitations of epidemiological study samples

Despite the strength of epidemiological evidence supporting a link between maternal infection, maternal immune activation and neurodevelopmental disorders, particularly ASD and SCZ as highlighted in this review, we believe these studies come with limitations that should be discussed more frequently in the poly I:C MIA literature.

For starters, certain populations have been overrepresented in the epidemiological literature that we summarized in **Table S1**, as can be seen under the Country + birth sample column. A quick glance at this column shows how most of these studies have been performed in select European countries (Denmark, Finland and Sweden) or in the United States. For studies performed in the United States, the Child Health and Development Study (CHDS) and the closely related Prenatal Determinants of Schizophrenia Study (PDS) have been utilized several times. While databases such as CHDS, PDS and the Danish National Birth Cohort are excellent sources of information, they represent geographically distinct populations which may be associated with specific genetic or environmental factors that can modulate susceptibility to the effects of maternal infection. For example, maternal diet is one factor that may be modulate resilience or susceptibility to MIA (Meyer, 2019) and can vary greatly by region. Another glance at the same column in **Table S1** also shows that most samples are temporally restricted to the mid to late 20th century, although more recent studies have begun including subjects born from 2000 onwards. On one hand, this restriction is necessary for exposures such as the 1957 Influenza pandemic and given the time it takes for patients to be diagnosed with ASD or SCZ. However, commonly used databases such as CHDS and PDS only followed births occurring between 1959 and 1966. Since 1966, environmental factors such as diet or healthcare, even within the same population where these studies were originally conducted, could have changed substantially. While we think discussing limitations of epidemiological samples is important within the MIA field, we believe it is perhaps more crucial to highlight what makes such studies an incredibly valuable source of information (e.g collection of maternal sera) and use such discussions to launch similar prospective studies that will allow researchers in the future to better understand neurodevelopmental disorders.

The last feature of epidemiological studies we would like to highlight is diagnosis. Although we did not include this information in our table (see Khandaker et al., 2013 for example), the

referenced studies have either used the International Classification of Diseases (ICD) or the Diagnostic and Statistical Manual for Mental Disorders (DSM) for classifying the subjects' diagnosis of ASD or SCZ, with exact versions of ICD or DSM depending on when the study was conducted. The ICD and DSM share many similarities in diagnosis of ASD and SCZ, but differences in diagnostic criteria exist across the two manuals and between different versions of the same manual, which may be of importance when considering older epidemiological literature (Biedermann and Fleischhacker, 2016; Doernberg and Hollander, 2016). In our review of the epidemiological literature, we have highlighted some studies where associations with maternal infection were dependent on the precise diagnosis, and these studies are marked with an X symbol in **Table S1**.

Evidence for pathogen-specificity

The MIA hypothesis is supported by associations of ASD and SCZ diagnosis with multiple types of infectious diseases, as well as with immune markers common to a variety of infections. However, there is still evidence for pathogen and cytokine specificity (relevant literature marked with ♦ in **Table S1**). For example, although Buka et al., (2001) and Mahic et al., (2017) investigated a variety of prenatal infections for association with SCZ and ASD risk, respectively, both studies only found a significant association for HSV-2 but not HSV-1, CMV or rubella. Similarly, but in context of cytokines, Brown et al., (2004) found an association between second trimester IL-8 but not IL-6 or TNFα with offspring SCZ. This line of evidence is a reminder that there much to learn from maternal infection models and models that induce different types of immune stimulation beyond the commonly used poly I:C or LPS injections.

2.2 Translation of brain development across species

From a translational perspective, it is essential to compare and contrast developmental timelines between humans and rodents, the most commonly used preclinical model in poly I:C MIA. Furthermore, developmental timeline variations between rats and mice – the two most commonly used species – must be considered when analyzing and comparing results from MIA literature. MIA models administer a controlled level of immune challenge at a specific time point during gestation. Precise control of the level of immune challenge is one of the main reasons why MIA models were initially chosen over infection models (Cunningham et al., 2007; Meyer et al., 2009).

The time point of MIA during gestation is critical since developmental processes occurring at or shortly after the time of MIA administration will be most impacted.

Human-rodent comparison

Epidemiological studies show the strongest offspring risk associations with first and second trimester maternal infections. Therefore, in most rodent poly I:C MIA studies the immune challenge is administered at the rough developmental equivalent in rodents, a period from gestation day (GD) 9.5 to GD18.5, out of a total gestation length of 20-22 days. Developmental differences, however, cannot be easily generalized across all organ systems or even within one organ such as the brain. Based on the multi-species translational model developed by Workman et al (2013), we have classified brain developmental events and constructed a figure that roughly summarizes these processes in rats, mice and humans (**Figure. 1**). At first glance, it is quite apparent that prenatal and postnatal development differ widely between rodents and humans. For example, while cerebral neurogenesis and cortical layering is almost complete before birth in humans, it continues postnatally in both rats and mice. Additionally, the onset of rapid synaptogenesis occurs prenatally in humans but postnatally in both rats and mice, which means MIA experiments are inherently unable to model developmental disruptions in this type of process. Postnatal immune activation has been attempted in rodents for these later developmental events (Baghel et al., 2018; Custódio et al., 2018; Majidi et al., 2016), but this lacks the maternal-fetal interface which plays a large role in modulating the extent of immune signaling that reaches the fetal brain (Hsiao and Patterson, 2012).

Linking MIA's effects to distinct developmental processes in rodents is difficult, especially given the large number of simultaneously developing structures, particularly during early gestation (**Figure 1**). Historically, MIA studies have tended to base their poly I:C MIA timing on epidemiological associations and translation of those timings into rodents, rather than targeting specific prenatal developmental processes.

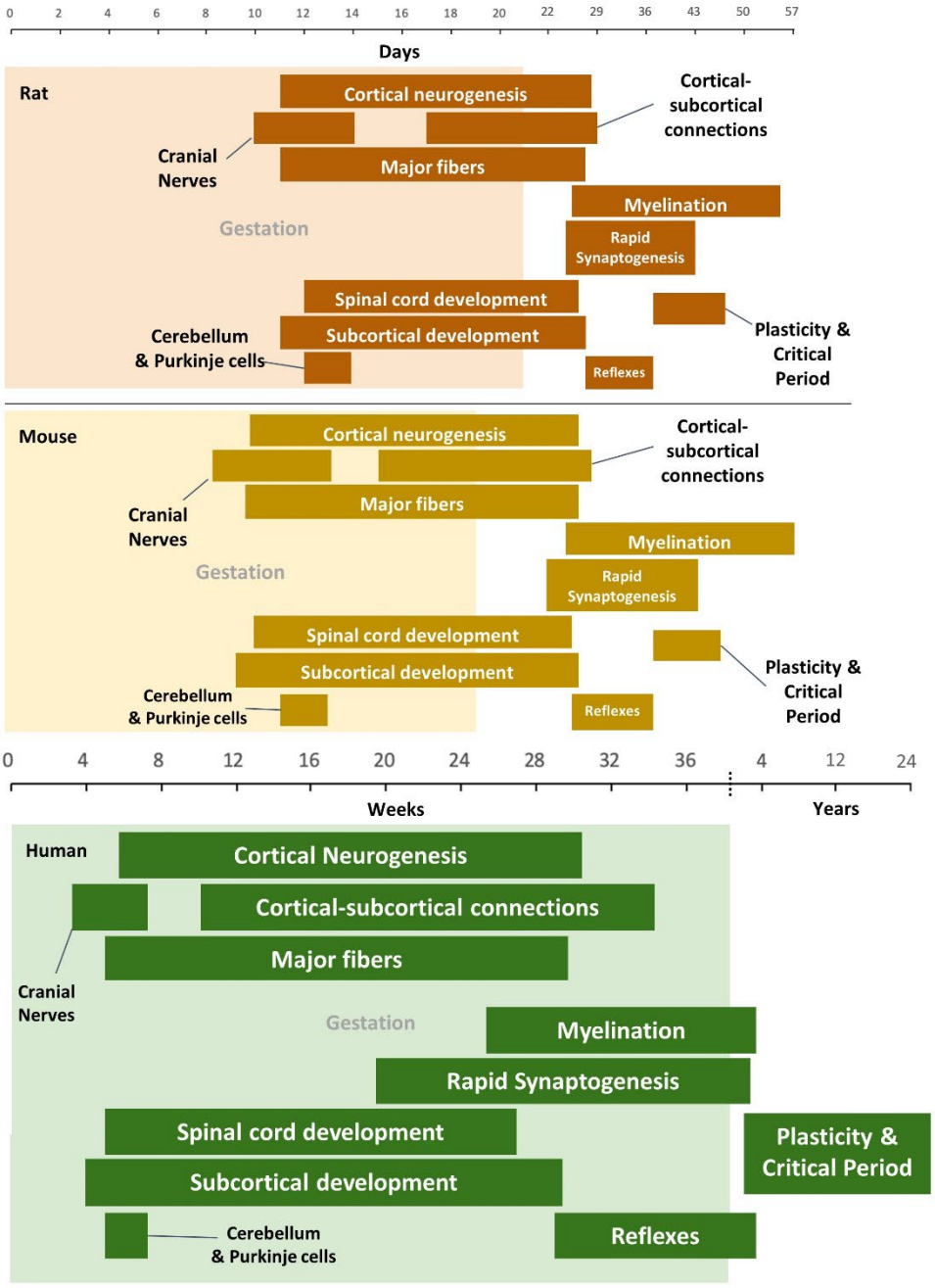

Figure 1. Developmental timeline comparison between humans, rats and mice adapted from the multi-species model by Workman et al. (translatingtime.org)

Rat-mouse comparison

Most poly I:C MIA studies have been conducted in either rats or mice. While these two species share phenotypic similarities, their embryonic brain developmental timelines are offset on average by 1-2 days, with rats exhibiting slower development starting 8 or 9 days post conception (Altman

and Katz, 1962; Workman et al., 2013; **Figure. 1**). These differences must be accounted for when attempting to replicate a mouse study in rats or when contrasting rat and mouse studies performed at the same gestation day. In addition, it is important to note the difference between the term gestation day (GD) and embryonic day (E), as well as how different researchers define those terms. In our review, we have attempted to reclassify all referenced work to the same timing convention as far as respective information was provided. Here, mid-day post conception - the day a vaginal plug is typically found - is designated as GD0.5.

Macaque MIA, a new wave of studies

In recent years, a new wave of studies has sought to determine the effects of infection and immune activation in Rhesus macaque monkeys. These studies were driven by a need for closer translatability to humans in both brain development and the range of measurable phenotypes. For example, such studies allow researchers to study the effects of third human trimester immune activation on brain development, which is not possible in rodents whose equivalent developmental stages occur postnatally (Short et al., 2010). On the other hand, Rhesus macaque MIA studies have allowed the study of social behaviours not measurable in rodents, such as social attention and detection of facial expressions (Machado et al., 2015)

The translational model by Workman et al., (2013) exemplifies the similarity in prenatal brain maturation between humans and macaques. In fact, the timing of developmental events is generally conserved even after splitting either gestation by trimesters. For example, myelination and synaptogenesis events occur at the end of the second and beginning of the third trimester in both humans and macaques. Despite this congruency, even slight differences may be substantial to consider in future studies, given that the effects of poly ICLC, the monkey equivalent of poly I:C, are acute and typically undetectable in blood 5 days following the last injection (Bauman, Weir). Given sufficient time, the monkey MIA model will likely become more prevalent as evidence from existing cohorts continues to mount and methodological details are optimized.

Injection timing and frequency in poly I:C literature

As mentioned above, in most poly I:C experiments poly I:C was administered as early as GD9.5 and as late as GD18.5. In most studies a single poly I:C or vehicle injection was performed at a single time-point in all dams. In contrast, in a few studies a single poly I:C injection was administered, but at different days in separate cohorts, which allows for within-study comparison of the effects of poly I:C timing. This is a more reliable way of uncovering the effects of poly I:C

MIA timing in contrast to between-study comparisons, as more variables such as housing, animal care, poly I:C batch, etc.. are accounted for. Additionally, in some studies, poly I:C MIA injections were performed at multiple days throughout gestation in the same cohort. Using multiple injections makes it difficult to associate offspring effects to any one specific developmental event and do not necessarily recapitulate the time course of the majority of human infections which usually last for a short time period relative to the length of the pregnancy. However, they may still provide insight into underlying MIA mechanisms or the extreme effects of inflammatory conditions on fetal brain development.

2.3 Poly I:C: A viral immune stimulant

Poly I:C is synthetic analog of double-stranded RNA (dsRNA) composed of homo-polymers of inosine and cytidine nucleotides. The dsRNA molecular pattern is commonly found in viral replication cycles, particularly of dsRNA viruses, single stranded RNA viruses and double stranded DNA viruses (Lester and Li, 2014; Weber et al., 2006). Mammalian immune systems have evolved to detect dsRNA through the innate immune receptor Toll-like-Receptor 3 (TLR3). Binding of poly I:C to TLR3 elicits pro-inflammatory downstream signaling with ensuing activation of the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) and Interferon (IFN) Regulatory Factor (IRF3) pathways (Takeda, 2004). Ultimately, these signaling cascades result in the expression of pro-inflammatory cytokines that travel through the bloodstream and trigger cellular and molecular changes in a variety of different cell types including neurons and glia (Deverman and Patterson, 2009).

While downstream signalling of different TLRs is similar, differences still exist between them. For example, type-I interferons are induced by TLR3 and TLR4 activation but not by TLR2 and TLR5 activation, whereas TLR7, 8 and 9 induce type-I interferons through different mechanisms (Takeda and Akira, 2005). Therefore, TLR3 activation is not reflective of the same innate immune response elicited by all infectious agents that have shown epidemiological associations. In the context of viral infections, TLR7 and TLR8 bind viral single stranded RNA such as that in influenza and activate slightly different interferon signaling compared to TLR3 (Kawai and Akira, 2011; Lester and Li, 2014). Beyond the mere activation of TLRs and associated downstream signaling, the expression pattern of these TLRs in different tissue may also play a role in their impact on fetal neurodevelopment. For example, while TLR3 is expressed in a variety of tissues, placental expression of TLR3 is one of the highest amongst all human tissue types, unlike TLR4 and TLR7

which are highest in the spleen (Nishimura and Naito, 2005; Zarember and Godowski, 2002). This places TLR3 in closer proximity to the maternal-fetal interface and suggests that the effects of activating different TLRs may produce phenotypes driven by different underlying mechanisms. Indeed, a recent study by Missig et al. (2019) has shed light on differential TLR activation in the context of MIA, showing that MIA using the TLR7 agonist imiquimod may produce profoundly different effects compared to poly I:C or LPS MIA.

In rodents, the immune response elicited by poly I:C is acute, with elevated individual cytokine levels following a specific time course for up to 48 hours after injection (Cunningham et al., 2007; Fortier et al., 2004; Meyer et al., 2009). Specific cytokines within this response such as IL-6, IL-1β, and TNFα are considered crucial for the effects of poly I:C MIA. Studies have shown that administering these cytokines alone may be sufficient in reproducing poly I:C MIA effects in the offspring (Garbett et al., 2012; Smith et al., 2007), and that poly I:C MIA effects can be blocked by antagonizing these cytokines during, or prior to, poly I:C administration (Lammert et al., 2018; Lipina et al., 2013; Pineda et al., 2013; Smith et al., 2007).

Despite the large number of preclinical studies that have utilized the poly I:C MIA model to investigate neurodevelopmental disorders, interpretation is not straightforward due to the variability in MIA parameters and experimental conditions between studies, which has been previously brought to light (Meyer et al., 2009) and has been gaining more recent attention (Careaga et al., 2018; Mueller et al., 2018). Extent, timing and duration of MIA exposure are critical, although other variables such as animal sex, strain and age during testing can all influence offspring results and their effects will be discussed in later sections.

2.4 Poly I:C experimental variables

Results from poly I:C MIA experiments have, at times, proven difficult to replicate when MIA is performed at the same gestational timing. An example of this variability can be seen in later sections of this review but is more specifically highlighted in a review by Smolders et al., (2018), who discussed some conflicting evidence for microglial phenotypes in poly I:C and other MIA models. Experimental variables that influence the outcome of poly I:C MIA experiments have been discussed in detail elsewhere (Careaga et al., 2018; Kentner et al., 2019; Meyer et al., 2009; Mueller et al., 2019). Variables such as route of administration, dose and length of the poly I:C molecule are crucial in determining the extent of the immune response elicited by the animals. Beyond poly I:C administration, offspring variables such as age, sex also play a role in

determining the phenotype elicited by poly I:C MIA, as evidenced by later sections of this review that report poly I:C phenotypes in context of these variables.

Poly I:C exposure categories: In our attempt to group and summarize the results of poly I:C literature, we have divided poly I:C studies based on poly I:C exposure timing categories. Each category contains studies with similar poly I:C injection timing, dose, routes of administration and model species used. Injection timing and the extent of the maternal immune response are critical, as each exposure category essentially represents a different model targeting distinct developmental processes to different extents. Much of the poly I:C literature has tended to follow initial findings by Meyer et al. (2006) and Zuckerman et al. (2003) who used mouse MIA at GD9.5 and 17.5, and rat poly I:C models at GD14.5, respectively. Based on the promise and high face validity shown by those early studies, the rest of the field followed suit, with about two thirds of the studies examined in this review sharing highly similar poly I:C dose, route of administration, and model species with those early studies. Later on, a new mouse model with poly I:C injections at GD12.5 was introduced with new insights into MIA phenotypes and mechanisms .

2.5 Offspring variables: Age, sex and strain

Besides maternal environment and immune responsiveness, offspring variables such as age of testing, sex of the offspring, and animal strain used can also influence results and have implications for the model's validity, particularly in modeling ASD and SCZ. These two disorders manifest differently throughout age, and they both seem to preferentially affect males (Mendrek and Mancini-Marïe, 2016; Werling and Geschwind, 2013). Additionally, different rat and mouse strains exhibit varying degrees of specific postnatal behaviours such as e.g. exploration or sociability (Moy et al., 2007). Recently, a study conducted by Kim et al. (2017) showed that mice obtained from different suppliers can respond extremely differently to poly I:C MIA, and this was attributed to differences in their gut microbiome. These differences may mask or exacerbate the effects of prenatal poly I:C. In reviewing each poly I:C exposure category in its respective table and results summary section, we have closely examined age, sex and strain-specific effects. Later sections will also discuss age and sex-specific effects more closely.

3. Methodological and Results Summary

3.1 Poly I:C MIA in Early Gestation (GD8.5-9.5)

The earliest poly I:C injections have been performed around GD8.5-9.5. The majority of these studies were done in mice, with only a handful using rats. In terms of poly I:C doses and routes of administration, the most common injection is 4-5 mg/kg of poly I:C administered intravenously, although there are several studies that injected different doses up to a maximum of 60 mg/kg, with higher doses typically being injected intraperitoneally. Offspring results have been observed with intravenous injections as low as 2mg/kg (Meyer et al., 2010, 2008, see **Table 1** for most common early poly I:C procedures in mice). The majority of early poly I:C studies also investigated adult offspring phenotypes, with only some investigating juvenile and adolescent rats, and very few testing multiple ages in the same offspring.

The most consistent behavioural findings in offspring exposed to early prenatal poly I:C seem to be decreases in prepulse inhibition (PPI) of the acoustic startle response (Fukudome et al., 2018; Giovanoli et al., 2013; Sandra Giovanoli et al., 2016; Hui et al., 2018; Kim et al., 2018; Lee et al., 2018; Li et al., 2009, 2015; Liu et al., 2013; Luan et al., 2018; Meehan et al., 2017; Meyer et al., 2008b; Meyer et al., 2010; Mueller et al., 2018; Pacheco-López et al., 2013; Richetto et al., 2017b; Song et al., 2011; Vuillermot et al., 2010, 2011; Weber-Stadlbauer, 2017), and decreased sociability (Buschert et al., 2016; Hui et al., 2018; Kim et al., 2018; Mueller et al., 2018; O'Leary et al., 2014; Richetto et al., 2017b; Vuillermot et al., 2017; Weber-Stadlbauer, 2017). The PPI deficit is also seen in studies that used higher poly I:C doses (Gonzalez-Liencres et al., 2016; Makinodan et al., 2008). Moreover, early MIA offspring tend to show an elevated response to amphetamine (Borçoi et al., 2015; Luan et al., 2018; Meyer et al., 2008; Meyer et al., 2008b, 2008a; Meyer et al., 2010; Missault et al., 2014; Vuillermot et al., 2010; Willi et al., 2013), although some conflicting reports exist (Buschert et al., 2016; Meehan et al., 2017).

The inflammatory brain phenotype in early MIA offspring is still relatively unclear. While some report no change cytokine and microglial phenotype in the hippocampus, frontal cortex and striatum (Duchatel et al., 2018b; Sandra Giovanoli et al., 2016; Meyer et al., 2008; Willi et al., 2013), others have found the presence of pathologically associated 'dark' microglia, in addition to findings of increased microglial clustering and reduced arborization (Hui et al., 2018). These microglial changes may also be dependent on testing age and poly I:C dose, as a couple of studies

suggest that used 20mg/kg i.p. injections and investigated adolescent brains or juvenile microglial cell cultures (Ikawa et al., 2017; Juckel et al., 2011). It is important to keep the limitations in using microglia as markers of inflammation in MIA studies in mind (Smolders et al., 2018b) and consider extending studies to other inflammatory changes such as those seen in the TLR and NRF2 pathways (MacDowell et al., 2017). Some volumetric brain changes have been reported including a decrease in brain volume and an increase in lateral ventricular volume (Abazyan et al., 2010; da Silveira et al., 2017; Li et al., 2009), In addition, early MIA offspring exhibit changes in different neurotransmitter (NT) systems that appear to be region-dependent. The hippocampus of early MIA offspring has shown reductions in serotonin levels and no changes in dopamine levels (Ohkawara et al., 2015; Winter et al., 2009). On the other hand, changes of striatal levels of these molecules have shown to be region-specific (Giovanoli et al., 2013; Ohkawara et al., 2015; Winter et al., 2009). Additionally, studies have shown alterations in receptor or cell-specific marker expression in various regions. This includes changes in neurotransmitter systems such as the dopaminergic (tyrosine hydroxylase, dopamine receptors 1 and 2, dopamine transporter), the glutamatergic (GluR1, mGlu2/3) and the GABAergic system (parvalbumin, GAD67, GABAAα2; Canetta et al., 2016; Corradini et al., 2018; Giovanoli et al., 2014; Harvey and Boksa, 2012; Holloway et al., 2013; Li et al., 2015; Meehan et al., 2017; Meyer et al., 2008b, 2008a; Nyffeler et al., 2006; Rahman et al., 2017; Vuillermot et al., 2010). The epigenetic profile of early MIA offspring includes changes in both histone acetylation and DNA methylation (Basil et al., 2014, 2018; Richetto et al., 2017b) and some changes are unsurprisingly associated with developmental gene networks (Basil et al., 2018; Richetto et al., 2017b).

Early poly I:C studies have attempted numerous treatments to try and rescue or prevent the effects of poly I:C on the offspring, with treatments such as cytokine antibody or anti-inflammatory drug administration at the same time as maternal poly I:C injection (Lipina et al., 2013; Song et al., 2011), IL-10 genetic upregulation (Meyer et al., 2008), maternal diet vitamin D supplementation (Vuillermot et al., 2017) or treatment of the offspring with the anti-bacterial drug minocycline (Giovanoli et al., 2016) or with various antipsychotics (MacDowell et al., 2017; Meyer et al., 2010; Shi et al., 2003). Almost all of these have been shown to alleviate some form of offspring behavioral symptoms such as deficits in PPI or LI, and some have even shown rescue of brain inflammatory phenotypes (see **supplementary Table S3**).

Double hit studies have also shown that early poly I:C MIA potentially interacts with peripubertal stress (Giovanoli et al., 2014, 2013; Giovanoli et al., 2016), maternal stress (Holloway et al., 2013), adolescent housing conditions (Buschert et al., 2016) and SCZ-related genetic deficiencies in Nuclear receptor related protein 1 (Nurr1; Vuillermot et al., 2011), Disrupted in Schizophrenia 1 (DISC1; Abazyan et al., 2010; Lipina et al., 2013) and Neuregulin-1 (NRG-1; Hemmerle et al., 2015) to produce a more severe phenotype (see section 3.8 for more details).

3.2 Poly I:C MIA in Mid-Gestation (GD12.5-13.5)

The next gestational stage where poly I:C MIA has been extensively investigated is at GD 12-13. Studies that have looked at this epoch almost exclusively utilized mice and a poly I:C dose of 20 mg/kg administered intraperitoneally. Moreover, the majority used adult offspring for their testing, with only a few papers testing their subjects at a juvenile (**Table 2**). Once again, doses as low as 2mg/kg may be sufficient to cause placental and offspring effects (Goeden et al., 2016; Naviaux et al., 2013). Interestingly, Tsukada et al. (2015) showed that poly I:C's effects may hit a ceiling as 4mg/kg and 20mg/kg poly I:C doses had highly similar effects on the fetal cerebral cortex and placental TLR3 signaling.

Behaviorally, this poly I:C offspring exposure group exhibits decreased PPI (Hsiao et al., 2013; Wu et al., 2017), anxiety-like behaviour measured through increased center activity in the open field, (Hsiao et al., 2013, 2013, 2012, 2012; Kim et al., 2017; Shin Yim et al., 2017; Wu et al., 2017) and deficits in social behaviour (Hsiao et al., 2013, 2012; Kim et al., 2017; Morais et al., 2018; Pendyala et al., 2017; Schwartzer et al., 2013; Weiser et al., 2016; Xuan and Hampson, 2014). Additionally, offspring consistently exhibit increased repetitive behaviour (Coiro et al., 2015; Hsiao et al., 2013, 2012; Kim et al., 2017; Morais et al., 2018; Pendyala et al., 2017; Schwartzer et al., 2013; Shin Yim et al., 2017; Wu et al., 2017; Xuan and Hampson, 2014) and alterations in ultrasonic vocalizations (USVs; Hsiao et al., 2013; Kim et al., 2017; Shin Yim et al., 2017; Weiser et al., 2016). Other behavioural results such as from the elevated plus maze, novel object recognition, light-dark test and reaction to amphetamine are less commonly investigated and more variable across studies.

Only few molecular results from early-mid poly I:C studies have been replicated, although some of these results have important implications. For example, changes in hippocampal excitatory postsynaptic currents (EPSCs) and long-term potentiation (LTP; Ito et al., 2010; Khan et al., 2014),

cortical and hippocampal histone epigenetics (Connor et al., 2012; Reisinger et al., 2016) and hippocampal microRNA profile have been shown, with the latter being related to rodent behavioural tests of motivation and anhedonia (Berger et al., 2018) Interestingly, these behavioural phenotypes seemed to persist across generations, a phenomenon that has received some attention in the MIA field and is reviewed elsewhere (Pollak and Weber-Stadlbauer, 2019). In the Prefrontal cortex (PFC), phenotypes include ASD-related cortical patches marked by the loss of cortical-specific markers Special AT-rich sequence-binding protein 2 (SATB2) and T-box, brain, 1(TBR1) (Shin Yim et al., 2017) and cortical changes in glutamate/gamma-aminobutyric acid (GABA) balance (Coiro et al., 2015). Beyond the brain, studies using this particular exposure have shown numerous non-neuronal and peripheral effects which support the notion that other organ systems are vulnerable to pe (Hsiao et al., 2013), increased peripheral IL-6 (Weiser et al., 2016), increased peripheral corticosterone(Majidi-Zolbanin et al., 2015) and changes in placental and splenocyte metabolism (Goeden et al., 2016; Schwartzer et al., 2013).

Several treatments have also been tested to alleviate or prevent these deficits, e.g. anti-purinergic suramin therapy and *B. fragilis* treatments have been attempted in the offspring (Hsiao et al., 2013; Naviaux et al., 2013). On the other hand, prevention attempts have included maternal anti-inflammatory agent administration and changes in maternal or offspring diet (Coiro et al., 2015; Kim et al., 2017; Smith et al., 2007; Weiser et al., 2016; Wu et al., 2015). Once again, most of these treatments have been successful at ameliorating or preventing behavioral phenotypes such as PPI deficits, increased repetitive behaviour, or USV impairments. Furthermore, genetic studies in mice have highlighted the role of the nicotinic receptor subunit (nAChRa7; Wu et al., 2015) and of IL-17 receptor subunit A (IL-17ra; Shin Yim et al., 2017) in the mechanism of early-mid gestation poly I:C MIA, wherein nAChRa7 and IL17a are both hypothesized to play a role in inducing poly I:C offspring phenotypes. Shin Yim et al. (2017) also showed that reducing activity in the dysgranular zone of primary somatosensory cortex rescued MIA behavioural deficits, whereas increasing activity in the same region induced these deficits in control animals.

3.3 Poly I:C MIA in Mid-Late Gestation (GD14.5-15)

The next major gestational time-point for poly I:C studies is GD14.5-15 and contains the majority of rat poly I:C studies in contrast to all other exposure times which mainly used mice (**Table 3**). Assuming rat development lags ~1.5 days behind that of mice, the time-point of GD14.5-15

equates to 13-13.5 in mice, not too far from the GD12.5 in mice. This is especially true considering that the poly I:C-induced immune response tends to last 24-48 hours. In terms of dose, most GD14.5-15 poly I:C rat studies have used an intravenous injection of 4 mg/kg or less commonly an intraperitoneal injection of 8-10mg/kg, again in contrast to the GD 12.5 mouse studies where intraperitoneal 20mg/kg doses dominate. In terms of offspring testing age, both adolescent and adult rats are commonly investigated, and many symptoms in this model only manifest in adulthood, emphasizing its resemblance with schizophrenia, and this observation is discussed further in section 3.6.

Behaviorally, GD14.5-15 poly I:C offspring consistently exhibit deficits in PPI (Bikovsky et al., 2016; Klein et al., 2013; Mattei et al., 2014; Osborne et al., 2017; Wolff and Bilkey, 2010, 2008; Yee et al., 2011) and latent inhibition (LI; Bikovsky et al., 2016; Piontkewitz et al., 2011a, 2011b; Zuckerman et al., 2003; Zuckerman and Weiner, 2005, 2003). In addition, these animals also exhibit increased responses to the dopaminergic agonist amphetamine and the glutamatergic N-methyl-D-Aspartate (NMDA) antagonist MK801 (Chou et al., 2015; Lins et al., 2018; Piontkewitz et al., 2011a, 2011b; Zuckerman et al., 2003; Zuckerman and Weiner, 2005, 2003), relating observed phenotypes to the hyper-dopaminergic and hypo-glutamatergic hypotheses of schizophrenia. Other behavioural phenotypes such as social behaviour, ultrasonic vocalization, and stereotypy are less commonly investigated, but some report deficits in these behavioural domains (Ballendine et al., 2015; Bates et al., 2018; Murray et al., 2017; Vernon et al., 2015; Wolff et al., 2011; Yee et al., 2012). Many of these studies investigated learning and memory in poly I:C offspring through various tasks including reversal learning, Y-maze, novel object recognition, temporal perception and odor span with evidence suggesting that GD14.5 rat offspring exhibit working memory deficits in a variety of contexts (Deane et al., 2017; Gray et al., 2019; Lins et al., 2018; Mattei et al., 2017; Murray et al., 2017; Osborne et al., 2017; Piontkewitz et al., 2011b; Vernon et al., 2015; Wallace et al., 2014; Wolff et al., 2011; Zhang et al., 2012; Zhang and van Praag, 2015).

Imaging studies have shown that while the whole brain volume is normal (Piontkewitz et al., 2011), significant region-specific changes exist including decreases in hippocampal and striatal volumes as well as increased lateral ventricular volume (Crum et al., 2017; Piontkewitz et al., 2011a, 2011b). In terms of molecular changes, the hippocampus has received a lot of attention with findings such as increased pro-inflammatory markers, cellular pyknosis and microglial activation

(Hadar et al., 2017; Mattei et al., 2017; Zuckerman et al., 2003; Zuckerman and Weiner, 2003) and alterations in glutamate decarboxylase (GAD) expression (Cassella et al., 2016), parvalbumin staining (Piontkewitz et al., 2012; Zhang and van Praag, 2015), neuronal nitric oxide levels (Zhang et al., 2018a), arginine metabolism (Jing et al., 2013; Zhang et al., 2018b) and postnatal neurogenesis (Chou et al., 2015; Zhang and van Praag, 2015). Cortical changes received less attention in GD14.5-15 poly I:C studies, but some published results include reduced coherence with the hippocampus (Dickerson et al., 2014, 2010), an altered entorhinal cortical transcriptome (Hollins et al., 2016), and the lack of an inflammatory phenotype (Hadar et al., 2017; Missault et al., 2014; Paylor et al., 2016; Van den Eynde et al., 2014).

Attempted treatments include typical/atypical antipsychotics (Patrich et al., 2016a; Piontkewitz et al., 2012; Richtand et al., 2011, 2012; Zuckerman et al., 2003; Zuckerman and Weiner, 2005) deep brain stimulation (Bikovsky et al., 2016; Hadar et al., 2017; Klein et al., 2013), administration of the antibiotic minocycline in drinking water (Mattei et al., 2017, 2014) and more recently, adolescent cannabidiol treatment (Osborne et al., 2017). Antipsychotics, minocycline, and adolescent cannabidiol treatments have all been able to rescue some of the behavioural phenotypes such as decreased LI or increased amphetamine reactivity seen in mid gestation MIA offspring (**supplementary Table S3**). As for deep brain stimulation, its beneficial effects were restricted to particular stimulation locations and parameters, with treatment targets including the Nucleus accumbens (NAc) and PFC.

3.4 Poly I:C MIA in Late Gestation (GD16.5-18.5)

The latest gestational time-point at which poly I:C has been administered is GD 16.5-18.5. In this category, the majority of studies injected 4-5 mg/kg of intravenous poly I:C in pregnant mice and tested adult offspring (**Table 4**). Numerous studies in this category also performed earlier poly I:C injections (typically GD9.5) in separate animal cohorts in order to compare the effect of gestational timing on offspring effects (Connor et al., 2012; da Silveira et al., 2017; Duchatel et al., 2016, 2018b, 2018a; Li et al., 2009, 2010; Meehan et al., 2017; Meyer, 2006; Urs Meyer et al., 2008b; Rahman et al., 2017; Richetto et al., 2017b)

Behaviourally, GD17.5-18 poly I:C offspring exhibit normal PPI (Li et al., 2009; Meehan et al., 2017; Meyer et al., 2008b; Richetto et al., 2017b), unlike offspring exposed to earlier MIA. They tend to show working memory impairments as measured by several different behavioral paradigms

(Connor et al., 2012; Krstic et al., 2012; Meyer, 2006; Meyer et al., 2010, 2008b; Richetto et al., 2017b, 2017a, 2014, 2013; Schwendener et al., 2009; Vuillermot et al., 2012). Notably, two studies reported enhanced LI (B. K. Bitanihirwe et al., 2010; Vuillermot et al., 2012), which stands in contrast to the impaired LI shown in GD14.5-15 offspring. Poly I:C offspring from this category also exhibit an elevated response to various psychoactive drugs including AMPH, MK801, cocaine, ketamine and apomorphine (Bitanihirwe et al., 2010; da Silveira et al., 2017; Labouesse et al., 2015; Meyer, 2006; Richetto et al., 2013).

Molecularly, most results come from single reports, including normal brain-wide histone deacetylase (HDAC) and DNA methyltransferase (DNMT) phenotype (Pujol Lopez et al., 2016), sex and subregion-specific effects in hippocampal GABAergic neurotransmission (Bitanihirwe et al., 2010; Luoni et al., 2017; Meyer et al., 2008b) and adult-onset effects on GABAergic but not dopaminergic neurotransmission in the cortex, with the latter negative finding being replicated in the striatum (Labouesse et al., 2015; Meyer et al., 2008b; Richetto et al., 2013, 2014). One study examined the cerebellum and reported a decrease in Purkinje cells (Naviaux et al., 2013).

Finally, GD17 MIA's effects have been shown to respond to chronic adult clozapine treatment (Meyer et al., 2010) and synergize with a Nurr1 genetic deficiency to produce attentional impairments and dopaminergic system alterations in the PFC and striatum (Vuillermot et al., 2012).

3.5 Repeated Poly I:C Administration

Most repeated exposure studies have administered poly I:C between GD10 to GD17, with several different methodologies including daily or alternate day administration. Poly I:C doses used across these studies tend to be around 4 mg/kg, typically administered intraperitoneally, and offspring testing age is variable with different studies investigating juveniles, adults, or different ages in the same cohort (**supplementary Table S2**). Results for these repeated administrations cannot be easily summarized, as the methodological differences in poly I:C administration have great implications for the severity, length, and overall effects of MIA on the developing fetus. They also cannot be attributed to any distinct developmental period event, due to the relatively condensed developmental timeline of rodent gestation. Multiple poly I:C administration paradigms also do not translate well into the human scenario as maternal infections do not last as long relative to the

length of the pregnancy. Nevertheless, these studies can still offer insight into MIA mechanisms and effects on fetal development.

The most common repeated poly I:C injection protocol seems to be a daily administration of poly I:C from GD11.5 to 16.5. Behaviourally, these studies have shown age- and prepulse-specific impairments in adult offspring PPI, no change in spontaneous locomotion (Han et al., 2016; Matsuura et al., 2018; Ozawa et al., 2006) and deficits in the novel object recognition test (NORT, Han et al., 2017, 2016; Matsuura et al., 2018; Ozawa et al., 2006). On the molecular level, these studies reported region-specific changes including, but not limited to, decreased parvalbumin (PV), altered amino acid and GABA/glutamate balance and decreased BDNF and trkB phosphorylation in the PFC and hippocampus, but not the NAc (Han et al., 2016).

3.6 Poly I:C in non-human primates

In 2010, the first study investigating the effects of third trimester maternal influenza infection in non-human primates, more specifically Rhesus macaques, was published (Short et al., 2010). While this study reported normal gestation length, birthweight and early life neuromotor and behavioural development, influenza exposed offspring showed cortical reductions in gray and white matter at 1 year of age. In the years that followed, LPS and poly ICLC (poly I:C adapted for use in primates) MIA models were also developed in macaques. In terms of gestational timing, the poly ICLC studies performed MIA at either the first or second trimesters of macaque gestation (Bauman et al., 2014; Machado et al., 2015; Rose et al., 2017; Weir et al., 2015), which is when prenatal infection in humans seems to confer the biggest risk. Much like the influenza study by Short et al., these studies reported normal early-life development in terms of physical growth, motor reflex development and interaction with mothers. However, as macaques aged to 6 months or older, they exhibited changes in repetitive behaviour (Bauman et al., 2014), social attention (Machado et al., 2015), cortical dendrite morphology (Weir et al., 2015), peripheral cytokines (Rose et al., 2017) and levels of striatal dopamine (Bauman et al., 2019). Some phenotypes such as abnormal social approach towards an unfamiliar animal at 6 months of age were specific to first trimester MIA and absent in second trimester MIA offspring. In terms of MIA dosage, the alterations in apical dendrite morphology at 3.5 years of age reported by Weir et al., (2015) were similar in offspring exposed to different doses of poly ICLC, although a small sample size warrants further investigation.

4. Discussion

4.1 Relevance to Neurodevelopmental Disorders: A Focus on ASD and SCZ

Cumulative evidence from the literature shows strong face and predictive validity of poly I:C MIA for ASD and SCZ-related symptoms. However, no single preclinical model is expected to replicate the entire spectrum of ASD and SCZ-related dysfunction, but certain animal models (in this case, offspring exposed to different MIA timings) may be more suitable than others for studying specific aspects of these complex disorders. In this section, we highlight a few phenotypes which are relevant to ASD and SCZ and identify poly I:C exposure categories which show relevant deficits.

Relevance to Schizophrenia

Dopaminergic hyperactivity: One prominent feature of SCZ is dopaminergic hyperactivity, as shown by the efficacy of typical antipsychotics in treating positive symptoms, which include hallucinations, delusions and disorganized though (Kahn et al., 2015). Dopaminergic hyperactivity is commonly tested in poly I:C offspring by measuring the response to amphetamine, a dopaminergic agonist. Poly I:C offspring of GD9.5 and GD17.5 mouse MIA, as well as GD14.5 rat MIA, have shown an increased locomotor response to amphetamine, indicative of dopaminergic hyperactivity. This is backed up molecularly in offspring of GD9.5 MIA and to a lesser extent in GD14.5 and GD17.5 MIA by region-specific changes in dopaminergic molecular markers such as dopamine metabolite levels, tyrosine hydroxylase and dopamine 1 receptor (Bitanihirwe et al., 2010; Luchicchi et al., 2016; Meyer et al., 2008b, 2008a; Vuillermot et al., 2012, 2010; Winter et al., 2009).

Ventricular enlargement, cortical thinning: Brains of individuals with SCZ tend to show ventricular enlargement and gray matter loss (Haijma et al., 2013), measures which have received attention mostly in GD9.5 and GD14.5 MIA offspring (Abazyan et al., 2010; Crum et al., 2017; da Silveira et al., 2017, 2017; Piontkewitz et al., 2011a, 2011b; Richetto et al., 2017a). These findings show that while total brain volume is not necessarily altered, region-specific decreases in gray matter, as well as increases in lateral ventricular volume, are present, potentially indicative of similar pathophysiological mechanisms between MIA and SCZ. In support of this notion and more directly implicating maternal inflammation, a study by Ellman et al. (2010) found that maternal IL-8 during pregnancy was correlated with increased ventricular volume and decreased

entorhinal cortex volume in adults with Schizophrenia Spectrum Disorder. Other neuroimaging findings relating maternal inflammation, ASD and SCZ, including a substantial number of poly I:C work, were recently summarized by Guma et al., (2019), who also discuss the limitations of translatability between human and preclinical findings.

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Relevance to Autism Spectrum Disorder

Social and repetitive behaviours: Behavioural symptoms of ASD mainly constitute social behaviour impairments, communication difficulties, and increased repetitive or stereotypic behaviour (Lai et al., 2014). Although the manifestation of social and repetitive behaviour is difficult to compare between rodents and humans, the same underlying mechanisms may be at play in determining sociability in both species. This notion is backed up by findings of social behaviour deficits in transgenic rodent models of ASD-risk genes (Möhrle et al., 2020; Verma et al., 2019). In poly I:C rodent offspring, preference for social contact is consistently impaired across all exposure categories (da Silveira et al., 2017; Hsiao et al., 2013, 2012; Hui et al., 2018; Kim et al., 2018, 2017; Konefal and Stellwagen, 2017; Marie Anaïs Labouesse et al., 2015; Lipina et al., 2013; Mattei et al., 2017; Mueller et al., 2018; Naviaux et al., 2013; O'Leary et al., 2014; Osborne et al., 2017; Pendyala et al., 2017; Richetto et al., 2017b, 2017a; Schwartzer et al., 2013; Shi et al., 2003; Vuillermot et al., 2017; Weiser et al., 2016). However, the strongest and most consistent evidence exists for GD9.5 and GD12.5 MIA offspring. Ultrasonic vocalizations in rodents are considered one way in which they communicate their emotional state and coordinate social interactions (Simola and Granon, 2019). Newborn offspring ultrasonic vocalizations —typically evoked by separation of pups from the dam in the first two postnatal weeks —are impaired following GD12.5 mouse poly I:C exposure and to a lesser extent GD14.5 rat MIA (Chou et al., 2015; Hsiao et al., 2013; Kim et al., 2017; Morais et al., 2018; Pendyala et al., 2017; Schwartzer et al., 2013; Weiser et al., 2016; Yee et al., 2012). Repetitive behaviour phenotypes, usually measured using the marble burying paradigm in rodents, follow a very similar trend to the previous two phenotypes: Many reports of increased marble burying in GD12.5 mouse offspring and very few studies investigating this measure other poly I:C exposure categories (Hsiao et al., 2013, 2012; Hui et al., 2018; Kim et al., 2017; Morais et al., 2018; Pendyala et al., 2017; Schwartzer et al., 2013; Vuillermot et al., 2017; Wu et al., 2015; Xuan and Hampson, 2014). Therefore, it is

important to not entirely rule out the existence of changes in repetitive behaviour and ultrasonic vocalization in later poly I:C exposures until further investigation.

Relevance to both Schizophrenia and Autism Spectrum Disorder

Historically, it took many years until ASD was differentiated from childhood schizophrenia (Evans, 2013). This early mix-up in diagnosis has since then been given some solace as ASD and SCZ are shown to have overlapping phenotypes and risk factors, with the prime example, in this case, being the maternal infection risk factor. Along the same lines, many of the changes that have been investigated in poly I:C literature such as PPI disruptions, cognitive dysfunction, brain inflammation and excitatory-inhibitory imbalance are common to both disorders.

Sensorimotor gating: Prepulse inhibition of the acoustic startle response is a staple operational measure of sensorimotor gating, the ability of an organism to pre-attentively filter out redundant sensory information. Decreased PPI is a hallmark of SCZ but has also been reported in ASD (Sinclair et al., 2017; Swerdlow et al., 2008). Poly I:C offspring from all the different exposure categories exhibit reductions in PPI, but the evidence is least consistent for GD17.5 mouse offspring (De Miranda et al., 2010; S Giovanoli et al., 2016; Gonzalez-Liencres et al., 2016; Hadar et al., 2017; Hsiao et al., 2013; Hui et al., 2018; Klein et al., 2013; Li et al., 2009; Mattei et al., 2014; U. Meyer et al., 2010; Richetto et al., 2017b; Song et al., 2011; Vuillermot et al., 2012; Weber-Stadlbauer et al., 2017; Wu et al., 2015). A broad PPI impairment across all exposure categories is perplexing but can be explained by the variety of structures that can have top-down modulatory effects on the PPI pathway (Bosch and Schmid, 2008, 2006; Fendt et al., 2001; Swerdlow et al., 2008). Therefore, while PPI is a valuable measure, conclusions about underlying mechanisms are limited without further investigation of PPI circuitry.

Cognitive deficits and excitation-inhibition imbalance: Cognitive deficits are common to both ASD and SCZ, and it is thought that excitation-inhibition imbalance may underlie cognitive changes in both disorders (Gao and Penzes, 2015). Evidence from poly I:C studies suggests that later MIA (GD14.5 and GD17.5) has a bigger impact on cognitive function compared to earlier poly I:C exposures and this phenotype is seen across a variety of behavioural tests including novel object recognition, Y-maze alternation and reversal learning (Connor et al., 2012, 2012; Gray et al., 2019; Krstic et al., 2012; Lins et al., 2018; Mattei et al., 2017; Meehan et al., 2017; Meyer, 2006, 2006, 2006; Meyer et al., 2010, 2008b; Mueller et al., 2018; Murray et al., 2017; Osborne et al., 2017; Piontkewitz et al., 2011b; Richetto et al., 2017b, 2017a, 2017b, 2014, 2013; Vernon et

al., 2015; Vuillermot et al., 2012; Wallace et al., 2014; Wolff et al., 2011; Zhang and van Praag, 2015). Moreover, numerous poly I:C studies have found molecular excitation-inhibition changes, particularly in GABAergic and glutamatergic neurotransmission. Findings include increased NMDAR binding following GD9.5 rat MIA (Rahman et al., 2017), and decreased GABA neurotransmitter levels as well as various GABAergic markers (GAD65, 67, PV and vGAT) following late MIA (B. K. Bitanihirwe et al., 2010; Cassella et al., 2016; Dickerson et al., 2014; Luoni et al., 2017; Urs Meyer et al., 2008b; Piontkewitz et al., 2011a; Richetto et al., 2013, 2014; Zhang and van Praag, 2015).

Immune dysregulation: Immune dysregulation, most commonly towards an inflammatory state, is also consistently reported in poly I:C offspring across different poly I:C exposures with measures including microglia, brain cytokines and TLR signaling (Duchatel et al., 2018b, 2018b; Garay et al., 2013; Sandra Giovanoli et al., 2016; Hadar et al., 2017; Hui et al., 2018; Juckel et al., 2011; Krstic et al., 2012; MacDowell et al., 2017; Mattei et al., 2014, 2017; Meyer et al., 2008; Murray et al., 2019; Paylor et al., 2016; Pratt et al., 2013; Smolders et al., 2015; Van den Eynde et al., 2014; Willi et al., 2013).

Overall, Poly I:C MIA shows very strong relevance to both ASD and SCZ, although the cumulative evidence shows that different aspects of these disorders are best translated by different gestational exposures. For example, ASD-related communication and stereotypic behaviours may be best studied with earlier immune activation, whereas cognitive impairments and inflammatory dysregulation are best investigated by later gestational exposures.

4.2 Correlation with the Extent of Maternal Immune Response

Perhaps the most crucial variable to control in MIA studies is the extent of the maternal immune response and how much of it is transmitted to the fetus. The immune response can vary across time and depends on housing conditions (Mueller et al., 2018), poly I:C source and lot number, and on its molecular weight (Careaga et al., 2018; Harvey and Boksa, 2012). Some studies also have even shown differential effects of poly I:C between different mouse strains (Morais et al., 2018;

Schwartzer et al., 2013). Therefore, quantification of the extent of the immune response should be a top priority to allow accurate comparison of offspring results across different studies.

Common immune response quantifications include: maternal temperature, maternal body weight gain, and the maternal serum cytokine profile. Out of these three variables, the maternal serum cytokine profile is the most accurate representation of poly I:C's potential effect on the fetus, given the mechanistic implications of cytokines such as IL-6 in MIA. While being currently the best measure for the extent of the maternal immune response, maternal cytokines are still only a surrogate measure of what the fetus is exposed to, and there is still potential for inter-fetal variability in the extent of exposure. An increase in maternal temperature and body weight gain following poly I:C are less direct measures of the extent of the immune response, and studies have not shown consistent reliability in using them as measures of the immune response (Ballendine et al., 2015; Howland et al., 2012; Murray et al., 2017; Sangha et al., 2014; Washington et al., 2015; Zhang et al., 2012). A study on sickness behaviour in response to poly I:C administration in mice reported hypothermia as opposed an increase in body temperature and argued this effect may be dose and species-specific (Cunningham et al., 2007).

Recent literature has begun to more regularly quantify the immune response in the dams whose offspring undergo testing, and some have attempted correlation with offspring phenotypes, with findings of no direct correlations of observed behavioral phenotypes with maternal serum cytokines, but a correlation with neonatal pup mass, which itself was related to maternal serum cytokines (Lins et al., 2018). Overall, quantification of the immune response in experimental or non-experimental animals is missing from a significant portion of the reviewed studies, leaving some doubt in the ability to directly compare results across studies.

Numerous studies have detected an elevated immune response in fetal tissue after maternal exposure to poly I:C (Abazyan et al., 2010; Arrode-Brusés and Brusés, 2012; Arsenault et al., 2014; Connor et al., 2012; Corradini et al., 2018; Ehninger, 2014; Meyer, 2006; Wu et al., 2015). These results come from separate dams whose offspring were not used for phenotyping and hence cannot be correlated to postnatal behavioural and molecular findings. However, measuring them can relate results across studies and help understand the variability or similarity in offspring findings.

4.3 An Eye Towards Mechanisms: Cytokines and the Developing Brain

The broad spectrum of phenotypes seen in poly I:C offspring show that its effects are not restricted to just one developmental process, brain region, or neurotransmitter system. This is further emphasized by the variety of treatments and preventions that have proven successful in ameliorating some or all the observed deficits (summarized in **Supplementary Table S3**). However, a special mention must be made to pro-/anti-inflammatory cytokine balance around the time of MIA. In particular, the pro-inflammatory cytokine IL-6 is often cited as essential to poly I:C's neurodevelopmental effects, which is unsurprising given the importance of IL-6 family cytokines and receptors in normal brain development (Deverman and Patterson, 2009). But how exactly does a change in IL-6 signaling alter brain development? IL-6 can either act directly on neurons and their precursors or it can activate glia which have their own developmental roles or may respond by producing more cytokines providing another level of signal amplification (Macht, 2016). Further support for the role of IL-6 in Poly I:C MIA comes from a study by Garbett et al. (2012) showing that the fetal brain transcriptomic overlap between IL-6, poly I:C and influenza MIA.

IL-6 and other cytokines such as leukemia inhibitory factor (LIF), ciliary neurotrophic factor (CNTF) and cardiotrophin-1 (CT-1) signal via receptors that contain glycoprotein 130 transmembrane protein (Deverman and Patterson, 2009). This activates downstream janus kinase (JAK) and signal transducer and activator of transcription 3 (STAT3), with the latter being a transcription factor that drives the effects of gp130 activation (Deverman and Patterson, 2009). Much like MIA's timing-specific effects, activation of gp130 signaling at different embryonic stages leads to diverse effects. Around GD12-15, gp130 signaling drives radial glial cell self-renewal (Gregg and Weiss, 2005; Hatta et al., 2002). Later in fetal development, gp130 signaling affects neural precursor cell fate and drives astrogliogenesis over neurogenesis (Koblar et al., 1998; Nakashima et al., 1999). In fact, neurons themselves produce CT-1 and as the number of neurons increases, the levels of CT-1 and thereby the push for astrogliogenesis also increases (Barnabé-Heider et al., 2005). Elevated IL-6 levels driven by poly I:C may therefore directly affect proliferation and differentiation of neural precursors. Despite all the IL-6 evidence, it must not be forgotten that the poly I:C immune response produces many different cytokines and chemokines which themselves might pale in contrast to the response induced by maternal infection. These other

immune response components such as IL-1β and TNF also have roles in nervous system physiology (Schafer et al., 2013; Schäfers and Sorkin, 2008), and their contribution to the broad spectrum of poly I:C offspring phenotypes is still far from clear.

Poly I:C MIA can also indirectly affect neuronal development and function by activating microglia, the brain's resident immune cells. Poly I:C studies have found changes in microglia both prenatally and postnatally (reviewed by Smolders et al., 2018), indicating that microglial function may be permanently altered by a single prenatal MIA insult. One explanation for this observation could be increased migration of macrophages destined to become microglia into the brain which is known to occur around GD8-10. This can be driven by changes in cytokines and chemokines such as macrophage-colony-stimulating factor (M-CSF) which has previously shown alterations following poly I:C injections (Arrode-Brusés and Brusés, 2012; Ehninger, 2014). M-CSF is required for the establishment of microglia in zebrafish (Herbomel et al., 2001) and also affects postnatal microglial number in mouse brains (Kondo et al., 2007; Sasaki et al., 2000). Additionally, microglia have other roles in the developing brain which include secreting neurotrophic factors (Garden and Möller, 2006) and synaptic pruning (Schafer et al., 2013). As a result, an increase in microglial number can have great implications for neurodevelopment not just at the time of MIA but much later on during postnatal development.

4.4 Maternal versus Fetal Effects and the Placenta

As poly I:C spreads throughout the maternal circulation, it can bind to TLR3 receptors which are expressed in a variety of tissues (Kawai and Akira, 2011; Nishimura and Naito, 2005). Interestingly, human work shows that TLR3 expression reaches some of its highest levels in the placenta (Kawai and Akira, 2011; Nishimura and Naito, 2005). With the placenta being in such proximity to the fetus, these high levels of TLR3 expression and their detection of poly I:C may be largely responsible for amplifying the MIA signal that reaches the fetal circulation and alters fetal brain development. In support of this hypothesis, poly I:C has been shown to induce increased placental immune activation via IL-6 and that blocking IL-6 signaling in placental trophoblasts can prevent the emergence of phenotypes in poly I:C offspring (Hsiao and Patterson, 2011). Recently, Tsukada et al., (2019) reviewed some mechanisms whereby MIA's effects can be mediated by the placenta, highlighting IL-6 and TNFα as modifiers of placental function, which in turn can alter fetal brain development. For example, MIA has been linked with reduced growth

hormone and increased levels of IL-6 production in the decidua, in addition to influencing placental spongiotrophoblast cells (Hsiao and Patterson, 2011; Wu et al., 2017).

Another potential layer of immune signal amplification is the fetal response to MIA, not just in the fetal brain but peripherally, although this is largely dependent on the extent of fetal immune development during the time of MIA. This is where MIA may be limited in replicating the human condition, as fetal immune development is quite delayed in rodents compared to humans (Holsapple et al., 2003). On the other hand, this simplifies the interpretation of rodent MIA results as they could be mostly attributed to the maternal immune response with little contribution of the fetal immune system.

4.5 Sex-Specific Effects in Poly I:C Literature

SCZ differentially affects males and females, with males showing earlier age of onset, more cognitive deficits, less response to antipsychotics, and greater changes in brain and ventricular volume (Mendrek and Mancini-Marïe, 2016). In some cases, SCZ patients show reversal of normal sexual dimorphisms in structural and functional phenotypes (Mendrek and Mancini-Marïe, 2016). ASD also preferentially affects males, but unlike in SCZ, it is not clear whether male and female phenotypes differ substantially (Werling and Geschwind, 2013). Nevertheless, the prevalence of ASD is much higher in males, with a ratio of almost 4:1. The extent to which sex differences were studied and the degree to which offspring sex impacted the effect of poly I:C vary across studies. In general, relatively few sex-specific effects are reported for all poly I:C exposure time points, with the proportion of studies that investigated both males and females is the lowest in the GD14.5 category.

In early GD9.5 MIA, a study by Hui et al. (2018) found male-specific changes in microglial activation, PPI and elevated plus maze, but not in social behaviour or marble burying. Meehan et al. (2017) also found decreased PPI specifically in males following early MIA in rats, whereas Rahman and colleagues (2017) reported increased cortical and striatal NR2A subunit binding in males but not females. There are few reports of sex-specific changes after GD12.5 poly I:C exposure despite most studies investigating both sexes and these include reduced latency to fall in the rotarod and increased marble burying (Pendyala et al., 2017; Schwartzer et al., 2013). At later MIA time points (GD14.5), decreased PPI, increased lateral ventricular volume, and increased set shifting errors are found in males only, in addition to differentially affecting male and female

hippocampal cell firing and response to AMPH and MK801 across age (Howland et al., 2012; Patrich et al., 2016a; Piontkewitz et al., 2011a). Late poly I:C MIA was found to cause sex-specific effects on neurotransmitter levels in various brain regions (B. K. Bitanihirwe et al., 2010) while another study by Duchatel et al. (2018a) reported increased complement 4 expression in the cingulate cortex of male GD9.5 poly I:C rat offspring. Taken together, while some have shown sex-specific effects, and particularly male vulnerability, following poly I:C MIA, the disparity between male and female phenotypes does not seem robust across studies and poly I:C exposure categories.

4.6 Age-Specific Effects in Poly I:C Literature

Since poly I:C models have typically been used to investigate ASD and SCZ, some attention must be given to the age of onset of brain and behavioural symptoms, which greatly differ between these two disorders. Whereas ASD symptoms appear very early on in the first few years of life, onset of SCZ symptoms is much later, with first episode psychosis occurring commonly in late teens or early adulthood, despite more subtle cognitive symptoms being present in the prodromal phase.

Most poly I:C studies examined changes in the adult offspring, particularly in the GD14.5 MIA studies, which is perhaps driven by early studies showing SCZ-like adult-onset behavioural changes in LI (Zuckerman et al., 2003; Zuckerman and Weiner, 2003). Interestingly, adult-onset decreases in PPI and LI are also reported multiple times in GD9.5 MIA offspring, which indicates that structures involved in modulating these two behavioural outcomes might be vulnerable at multiple stages of development (Giovanoli et al., 2016; Giovanoli et al., 2016; Lipina et al., 2013; Pacheco-López et al., 2013; Vuillermot et al., 2010). One early-onset behavioural phenotype that is more in line with MIA's relevance to ASD is altered pup-induced ultrasonic vocalization seen in both GD12.5 MIA mouse and GD14.5 MIA rat offspring (Chou et al., 2015; Hsiao et al., 2013; Kim et al., 2017; Pendyala et al., 2017; Schwartzer et al., 2013; Weiser et al., 2016; Yee et al., 2012). In contrast, non-behavioural outcomes seem to have earlier onset across different poly I:C exposure time points. For example, GD9.5 MIA offspring exhibit a decrease in cortical histone acetylation that is seen in as early as postnatal day (PND) 24 (Tang et al., 2013) and a decrease in cerebellar Purkinje cell density as early as 6 weeks of age (Shi et al., 2009). Similarly, GD12.5 MIA reduced cortical dendritic spines and increased surface MHCI proteins at PND17 (Coiro et al., 2015) and juvenile GD 14.5 MIA offspring showed altered hippocampal excitability and

increased glutamate/GABA ratio (Patrich et al., 2016a; Zhang et al., 2018b). In many cases, molecular phenotypes such as brain and peripheral cytokine levels are dynamic throughout postnatal development and do not necessarily persist until adulthood. A prominent example is seen wherein the vital proinflammatory cytokine IL-6 is downregulated at PND30 but upregulated at PND60 in the frontal cortex in GD12.5 MIA offspring (Garay et al., 2013). In contrast, later poly I:C exposures show adult changes such as increased lateral ventricular volume and decreased PFC expression of GABAergic markers GAD65, GAD67 and vGAT (Luoni et al., 2017; Urs Meyer et al., 2008b; Piontkewitz et al., 2011a; Richetto et al., 2014, 2013).

Overall, poly I:C seems to disrupt the brain at the cellular and molecular level generally early on in postnatal life, while behavioural outcomes often do not manifest until later, indicating that changes may accumulate until they reach a threshold in postnatal life where they manifest into behavioural symptoms. However, one must highlight that the age-specific effects do not follow the same trend for different MIA time points and are highly dependent on the type of behaviour and brain structure of interest.

4.7 Comparison with Lipopolysaccharides (LPS) MIA

The bacterial equivalent of poly I:C MIA is typically performed using injections of LPS which are components of gram-negative bacteria and activate the innate immune response similarly through Toll-like Receptor 4 (Takeda and Akira, 2005). Compared to the poly I:C MIA model, LPS MIA is more commonly done in rats than mice and the timing and frequency of LPS injections varies greatly. For example, LPS injections have been performed as early as GD7 and as late as the last day of pregnancy. Furthermore, numerous studies using LPS MIA perform multiple injections on consecutive or alternating days, and some even do injections throughout the entire pregnancy. This is in contrast to poly I:C MIA where the majority of studies perform a single acute immune activation.

Unlike poly I:C MIA which does not affect pregnancy outcomes (Fortier et al., 2007; Malkova et al., 2012; Morais et al., 2018; Vorhees et al., 2015; Vuillermot et al., 2011), LPS MIA seems to induce some obstetric complications, with some reports of increased preterm birth, reduced fetal viability and increased uteroplacental degradation and inflammation (Chang et al., 2011; Elovitz et al., 2011; Lee et al., 2013). This is highly relevant to the observation that SCZ and ASD are both associated with obstetric complications.

Behaviourally, GD9.5 LPS MIA induces ASD-like symptoms with increased stereotypy, altered communication and reduced social interaction (Fernández de Cossío et al., 2017; Foley et al., 2014; Fortunato et al., 2017; Imai et al., 2018; Oskvig et al., 2012). Moreover, changes in exploratory activity and an increase in anxiety and depression-like symptoms are also seen in early LPS MIA (Depino, 2015; Oskvig et al., 2012). Similar to poly I:C studies, later LPS MIA seems to show changes in working memory (Chlodzinska et al., 2011). PPI has not been as thoroughly investigated in LPS MIA studies as it has been in poly I:C MIA, although some reports of PPI deficits exist in studies that utilized multiple LPS injections throughout pregnancy (Basta-Kaim et al., 2012; Borrell et al., 2002; Harvey and Boksa, 2014).

On a molecular level, many changes mirror those observed in poly I:C MIA, with (prefrontal) cortex and hippocampus once again taking center stage. These include alterations in PFC GABAergic neurotransmission, hippocampal reelin immunoreactivity and brain/peripheral cytokine levels (Basta-Kaim et al., 2012; Boksa et al., 2016; Borrell et al., 2002; Clark et al., 2019; Depino, 2015; Elovitz et al., 2011; Guiraut et al., 2016; Harvey and Boksa, 2014; Imai et al., 2018; Lee et al., 2013; O'Loughlin et al., 2017; Rideau Batista Novais et al., 2013). Unlike poly I:C MA, there are few reported changes in dopaminergic phenotypes and more alterations are seen in GABAergic, Glutamatergic and serotonergic systems (Baharnoori et al., 2012; Batinic et al., 2017; Boksa et al., 2016; Connors et al., 2014; Depino, 2015; Hsueh et al., 2017; Oskvig et al., 2012). One extremely important finding in LPS literature that relates its mechanisms to poly I:C MIA is the dependency of prenatal LPS effects on IL-6, at least in context of postnatal hippocampal neurogenesis, shown by Mouihate (2016).

4.8 Double Hit Models

Double-hit models are based on the hypothesis that multiple risk factors, genetic and/or environmental, can synergize and lead to psychiatric disorders. Evidence of interaction between multiple genetic and environmental risk factors in SCZ includes changes in genetic liability under different contexts of urban environment and cannabis use, both of which are known environmental risk factors for the disorder (van Os et al., 2010). Others have argued that early life or adolescent stress may act as a second hit leading to the full adult phenotype (Picci and Scherf, 2015). Double or multiple-hit models represent a more holistic approach to understanding disorders with multiple risk factors and provide a fertile ground for linking these risk factors with common underlying

molecular pathways/mechanisms. The rapamycin (mTOR) signaling pathway in mammals exemplifies one such target, where numerous ASD risk genes converge, while external signals such as cytokines can also modulate this signaling pathway (Estes and McAllister, 2016). A comprehensive understanding of the interaction between different risk factors is key to designing more effective treatment and prevention plans for such complex disorders. Given poly I:C's mild effects on offspring viability and largely non-lethal phenotypes, it has potential for studying how prenatal inflammation can either act as an environmental first-hit, priming individuals for a later environmental insult, or as a second-hit in genetically predisposed individuals. Genetic factors used in combination with poly I:C include SCZ risk genes such as DISC1, Nurr1, NRG-1 and alpha 7 nicotinic acetylcholine receptor (ChRNα7).

Poly I:C MIA synergized with both DISC1 point mutations and mutated human DISC1 expression (Abazyan et al., 2010; Lipina et al., 2013) to exacerbate behavioural phenotypes such as PPI and anxiety-related behaviours in the elevated plus maze. However, this double-hit effect was dependent on the type of point mutation (Lipina et al., 2013) as well as the timing of expression of mutant human DISC1 (Abazyan et al., 2010), with the latter only occurring when mutant DISC1 was expressed post-weaning and not pre-weaning. Interestingly, one of the DISC1 point mutations which exhibited more behavioural double-hit effects with poly I:C also increased the fetal cytokine response after poly I:C. Poly I:C MIA also resulted in double-hit effects in Nurr1 heterozygous animals, which show reduced expression of Nurr1 and downstream dopaminergic markers, however, these double-hit effects were only present if poly I:C injections occurred during early (GD9.5) but not late (GD17.5) gestation (Vuillermot et al., 2012, 2011). The Nurr1+/- genotype also markedly influenced the immune response to poly I:C, reversing changes in IL-6 expression and eliminating changes in TNF IL-10 expression. Poly I:C MIA also interacted with NRG-1 (O'Leary et al., 2014) and ChRNα7 (Wu et al., 2015) genotypes to induce behavioural phenotypes such as open field exploration, PPI and Y-maze alternations.

Poly I:C MIA was also combined with environmental second-hit models including juvenile/peripubertal stress, adolescent cannabinoid exposure and experimental autoimmune encephalitis (as a model for Multiple Sclerosis). In terms of adolescent stress, double-hit effects were shown with GD9.5 mouse poly I:C MIA (Giovanoli et al., 2014, 2013; Giovanoli et al., 2016), whereas GD14.5 rat MIA only exhibited independent single-hit effects (Yee et al., 2011). This indicates that the timing of poly I:C exposure might be crucial, and that early MIA affects pathways

related to adolescent stress. Additionally, these studies also found that offspring phenotype changes with age. In adolescence, double-hit effects included increased hippocampal expression of pro-inflammatory markers, whereas in adult animals double-hit symptoms included PPI impairments, increased response to AMPH and changes in hippocampal parvalbumin and Reelin expression. Studies investigating double-hit effects with cannabinoid exposure utilized the Cannabinoid receptor 1 (CB1) agonist HU210 and administered it for 2 weeks starting PND 35 (Hollins et al., 2016, 2014; Idrizi et al., 2016). The main findings were changes in entorhinal cortex gene expression, microRNA profile and striatal epidermal growth factor receptor expression.

Overall, multiple studies indicate that poly I:C MIA can interact with other genetic and environmental risk factors to exacerbate both cellular and behavioural symptoms related to SCZ in the offspring. The indirect interplay between developmentally relevant genes and prenatal inflammation is evident in DISC1 and Nurr1 studies, where a heterozygous genotype is sufficient to alter the fetal immune response to poly I:C, pointing towards a common basic pathophysiological mechanism. The link with inflammatory signaling is even more direct in the context of adolescent stress, which itself induces postnatal inflammatory signaling. Prenatal priming of the immune system might persist postnatally and is able to interact with adolescent stress to manifest symptoms which otherwise would not show up. Poly I:C double-hit models therefore have shown considerable face validity in investigating more complex etiological mechanisms of disorders such as ASD and SCZ.

5. Conclusions

The history of poly I:C MIA in context of neurodevelopment started around 15 years ago and has continued to gain momentum ever since. The model has numerous strengths that make it extremely attractive for translational research. It has high construct validity as it replicates a well-established risk factor for neurodevelopmental disorders in maternal infection. Upon its use in preclinical rodent models, it shows considerable face and predictive validity, replicating several hallmarks of disorders such as ASD and SCZ as well as responding similarly to known treatments in humans. In addition to its validity, its downstream effects with regards to inflammation link it with numerous other neurodevelopmental risk factors such as early life stress, which means it can help uncover common underlying pathophysiological mechanisms of disorders such as ASD and SCZ. In support of this view, poly I:C MIA has been shown to synergize with both environmental and

genetic risk factors, making the offspring more vulnerable to various types of impairments in adolescence and adulthood. This kind of complex multi-risk study is mainly possible because of an inherent strength of the model: the ability to manipulate the timing and extent of the immune response to sufficiently but not excessively target specific developmental stages.

Just like any model, however, there are important limitations of the poly I:C model and crucial factors to consider when planning poly I:C experiments and interpreting results from the poly I:C MIA field. While a multitude of studies have been performed with poly I:C, the attempt to summarize results often proves difficult as methodological differences in dose, poly I:C strand length, route of administration, gestational timing, and choice of species can all produce critical variation in the effects of poly I:C MIA on the fetal brain. This is especially true given the relatively condensed developmental timeline in rodents, wherein a single day can encompass an enormous amount of structural and functional brain maturation. This methodological difficulty can explain some of the variation or inconsistencies in results, as it is discussed in most poly I:C MIA publications.

Despite a large body of work that has elucidated the phenotype of poly I:C MIA offspring, there is still much to learn about its pathophysiological mechanism. An example of such area that still needs clarification is the precise contribution of the maternal, placental and fetal compartments to the production of, and response to, cytokines which are thought to be the main mediators of poly I:C MIA's effects on the fetal brain. Nevertheless, poly I:C MIA has proven to be neurodevelopmental model with substantial validity and tremendous potential.

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Table 1: Offspring phenotypes after single poly I:C exposure in early gestation (GD9 to GD9.5), most commonly performed in mice

Exposure Details	References	Phenotypes (↑ increase, ↓ decrease, ≈ no change, NA no evidence available)		
Species Mouse **Timing** GD9-9.5 **Dose** 1-5mg/kg (most studies) or 20-60mg/kg **Route** i.v for most 1-5mg/kg injections i.p. for most 20-60mg/kg injections	**1-5mg/kg** Abazyan et al., 2010; Basil et al., 2014, 2018; Borçoi et al., 2015; Canetta et al., 2016; da Silveira et al., 2017; Deng et al., 2011; Duchatel et al., 2018b, 2018a; Giovanoli et al., 2013, 2014; Giovanoli et al., 2016; Giovanoli et al., 2016; Holloway et al., 2013; Hui et al., 2018; Kim et al., 2018; Lee et al., 2018; Li et al., 2009, 2010, 2015; Lipina et al., 2013; Luan et al., 2018; MacDowell et al., 2017; Meyer et al., 2005; Meyer, 2006; Meyer et al., 2006; Meyer et al., 2008; Meyer et al., 2008b, 2008a; Meyer et al., 2010; Mueller et al., 2018; Nyffeler et al., 2006; O'Leary et al., 2014; Pacheco-López et al., 2013; Richetto et al., 2017b; Shi et al., 2003; Tang et al., 2013; Vuillermot et al., 2010, 2011, 2017; Weber-Stadlbauer et al., 2017; Willi et al., 2013; Winter et al., 2009 **20-60mg/kg** Buschert et al., 2016; Corradini et al., 2018; Fukudome et al., 2018; Gonzalez-Liencres et al., 2016; Harvey and Boksa, 2012; Ikawa et al., 2017; Juckel et al., 2011; Liu et al., 2013; Makinodan et al., 2008; Shi et al., 2009; Soumiya et al., 2011	**Cellular and Molecular**	**Metabolic, Immune**	≈ brain and peripheral cytokines. ↑/≈ microglial activation. ↑ TLR3 signaling.
			NT Systems, Synapses & Electrophysiology	≈ global NT/metabolite levels. ↑ NMDAR binding in the cingulate and male striatum. ↓ D1R and PV GABAergic transmission into pyramidal cells. ↑ 5HTA2R and ↓ mGlu2/3 density in frontal cortex. Age and region-specific ↑/↓ Dopamine transporter, receptors 1/2 and tyrosine hydroxylase. **20mg/kg injection** ↑ # and ↓ heterotopy in cerebellar purkinje cells, altered neurogenesis in olfactory bulb but not Hippocampus
			White Matter	↓2',3'-Cyclic-nucleotide 3'-phosphodiesterase (CNPase) staining. Region-specific ↑/↓ in fractional anisotrophy but ≈ white matter volume
			Morphology, Imaging, Development, Neurogenesis	≈ cellular morphology and whole brain white/grey matter. ↑ Lateral ventricle volume. ↓ AKT (protein kinase B) in the PFC. ↑ Reelin+ cells in Hippocampus.
			Genetics epigenetics	Altered epigenetics and associated gene transcription. ↓ DNA methylation (hypothalamus, PFC), ↓histone acetylation (Cortex, Hippocampus).
		Behavioural	**Sensorimotor gating, exploration, anxiety**	Adult-onset ↓ PPI and LI. ↑ anxiety in open field.
			Social Behavior, USVs	↓ Sociability.
			Psychoactive drug response	Consistent ↑ response to AMPH. Response to other drugs also affected but fewer studies (↑/≈ MK-801, ↑2,5-Dimethoxy-4-iodoamphetamine (DOI), ↑ketamine, ↑ cocaine).
			Stereotypy	Two studies: ↑/↓ marble burying.
			Depression Symptoms	↑/≈ immobility in forced swim test. ↓ sucrose preference.
			Learning & Memory	↓/≈ memory in Y-maze, NORT, Morris Water Maze and fear conditioning.

Table 2: Offspring phenotypes after single poly I:C exposure in mid-gestation (GD12 to GD12.5), most commonly performed in mice

Exposure Details	References	Phenotypes (↑ increase, ↓ decrease, ≈ no change, NA no evidence available)		
Species Mouse **Timing** GD12-12.5 **Dose** 2-20mg/kg (most used 20mg/kg) **Route** i.p. except 2 studies (Ito and Connor)	Berger et al., 2018; Coiro et al., 2015; Connor et al., 2012; Garay et al., 2013; Garbett et al., 2012; Giulivi et al., 2013; Hsiao et al., 2013, 2012; Ito et al., 2010; Khan et al., 2014; Kim et al., 2017; Konefal and Stellwagen, 2017; Li et al., 2018; Majidi-Zolbanin et al., 2015; Missig et al., 2018; Morais et al., 2018; Naviaux et al., 2013; Onore et al., 2014; Pendyala et al., 2017; Pratt et al., 2013; Reisinger et al., 2016; Ronovsky et al., 2017; Schwartzer et al., 2013; Shin Yim et al., 2017; Smith et al., 2007; Smolders et al., 2015; Tsukada et al., 2015; Weiser et al., 2016; Wu et al., 2015; Xuan and Hampson, 2014	**Cellular and Molecular**	**Metabolic, Immune**	↑ prenatal microglial activation. ↑ postnatal brain MHCI. Strain-specific ↑ brain cytokines *Peripheral changes* in solenocyte metabolism, serum cytokines and corticosterone.
			NT Systems, Synapses & Electrophysiology	↑ glutamatergic mPFC-Basolateral amygdala projections, ↓ Hippocampal LTP and neurogenesis. ↓ glutamatergic synapse density in cerebellar purkinje cells. Somatosensory cortical activity underlies some behavioral deficits.
			White Matter	NA
			Morphology, Imaging, Development, Neurogenesis	↓ prenatal cortical volume and cell number. ↑ primary somatosensory cortical patches.
			Genetics epigenetics	Altered cortical transcriptome but not histone methylation. Generation-specific Hippocampal microRNA changes.
		Behavioural	**Sensorimotor gating, exploration, anxiety**	↓ PPI. ↑/≈ anxiety (open field).
			Social Behavior, USVs	↓ Sociability/Social novelty. ↓/↑ USVs.
			Psychoactive drug response	≈ AMPH reaction.
			Stereotypy	↑ marble burying
			Depression Symptoms	↑ immobility in forced swim test. Generation-specific ↓ in sucrose preference.
			Learning & Memory	↓ MWM, ≈ Y-maze, ≈ NORT.

Table 3: Offspring phenotypes after single poly I:C exposure in mid-late gestation (GD14.5 to GD15), most commonly performed in rats

Exposure Details	References	Phenotypes (↑ increase, ↓ decrease, ≈ no change, NA no evidence available)		
Species Rat except 2 papers by Zhang and Mattei **Timing** GD14.5-15 **Dose** 4-5mg/kg **Route** Rat studies i.v., mouse studies i.p.	Ballendine et al., 2015; Bates et al., 2018; Bikovsky et al., 2016; Chou et al., 2015; Crum et al., 2017; Deane et al., 2017; Dickerson et al., 2014, 2012, 2010; Farrelly et al., 2015; Gray et al., 2019; Hadar et al., 2017; Hollins et al., 2016, 2014; Howland et al., 2012; Idrizi et al., 2016; Jing et al., 2013; Klein et al., 2013; Lins et al., 2018; Luchicchi et al., 2016; Mattei et al., 2017, 2014; Millar et al., 2017; Murray et al., 2017; Osborne et al., 2017; Patrich et al., 2016a, 2016b; Paylor et al., 2016; Piontkewitz et al., 2012, 2011a, 2011b; Savanthrapadian et al., 2013; Van den Eynde et al., 2014; Verdurand et al., 2014; Vernon et al., 2015; Wallace et al., 2014; Wolff and Bilkey, 2010, 2015, 2008; Wolff et al., 2011; Yee et al., 2012, 2011; Zhang et al., 2018a, 2018b, 2012; Zhang and van Praag, 2015; Zuckerman et al., 2003; Zuckerman and Weiner, 2005, 20003	**Cellular and Molecular**	**Metabolic, Immune**	Region specific ↑ microglial activation, cytokine levels, hippocampus and striatum susceptible. Altered brain arginine and glucose metabolism.
			NT Systems, Synapses & Electrophysiology	Major focus on Hippocampal circuitry, changes include ↓ PV, altered neuronal excitability, ↓ coherence with PFC, ↓GAD67 and ↑ LTP persistence.
			White Matter	NA
			Morphology, Imaging, Development, Neurogenesis	≈ Total brain volume is unaffected Region-specific changed (↓Hippocampal and Striatal volume and ↑/↓ in ventricular volume) ↓ in Hippocampal cell #, ↑ pyknosis ≈ Hippocampal neurogenesis (BrdU/NeuN ratio)
			Genetics epigenetics	Changes in entorhinal cortex miRNA profile and transcriptome. Transcriptomic effects more severe in double-hit context with adolescent CB1 agonist exposure.
		Behavioural	**Sensorimotor gating, exploration, anxiety**	↓/≈ PPI. Adult-onset ↓ LI. Conflicting reports on open field exploration and startle reactivity phenotypes.
			Social Behavior, USVs	↓ social behaviour and USVs.
			Psychoactive drug response	↑ AMPH and MK801 response. MK801 age and maybe sex-specific.
			Stereotypy	≈ grooming.
			Depression Symptoms	↑ immobility in tail suspension test.
			Learning & Memory	↓ Reversal learning, Y-maze. ↓/≈ in NORT. ≈ MWM and fear conditioning. Some effects in other less common tasks such as odor span task or auditory temporal perception task.

Table 4: Offspring phenotypes after single poly I:C exposure in late gestation (GD16.5 to GD18.5), commonly performed in both rats and mice

Exposure Details	References	Phenotypes (↑ increase, ↓ decrease, ≈ no change, NA no evidence available)		
Species Mouse except 3 studies with rat **Timing** GD16.5-17.5 except rat studies which performed MIA at GD18.5 **Dose** 4-5mg/kg except Vuillermot et. al study which used a 2mg/kg dose **Route** i.v. except De Miranda et al., 2010 i.p.	Bitanihirwe et al., 2010a; Bitanihirwe et al., 2010b; Connor et al., 2012; da Silveira et al., 2017; De Miranda et al., 2010; Duchatel et al., 2018b, 2018a, 2016; Krstic et al., 2012; Labouesse et al., 2015; Labouesse et al., 2015; Li et al., 2010, 2009; Luoni et al., 2017; Meehan et al., 2017; Meyer, 2006; Meyer et al., 2010, 2008b; Pujol Lopez et al., 2016; Rahman et al., 2017; Richetto et al., 2017a, 2017b, 2014, 2013; Schwendener et al., 2009; Vuillermot et al., 2012	**Cellular and Molecular**	**Metabolic, Immune**	↑ postnatal brain inflammation in aged offspring.
			NT Systems, Synapses & Electrophysiology	↓ in GABAergic markers (GABA levels, GAD65, GAD67, GABA alpha subunits, PV, and VGAT) in the Hippocampus and PFC. Region-specific ↑ in NMDA receptor subunits such as NR2A. Disrupted Dopamine signaling (TH, COMT, Dopamine receptors), variable across studies.
			White Matter	≈ white matter volume. ↓fractional anisotrophy, CNPase staining, MOBP staining and myelin water fraction.
			Morphology, Imaging, Development, Neurogenesis	↓ postnatal neurogenesis. ↓/≈ brain volume.
			Genetics epigenetics	Alterations in gene expression related to GABAergic signaling and neuronal differentiation. Altered DNA methylation but not histone acetylation or histone methylation
		Behavioural	**Sensorimotor gating, exploration, anxiety**	↓/≈ PPI, variable across studies
			Social Behavior, USVs	↓ Sociability
			Psychoactive drug response	↑ response to AMPH, MK801, cocaine, ketamine and Apomorphine
			Stereotypy	NA
			Depression Symptoms	↓ Sucrose preference
			Learning & Memory	↓ working memory in Y-maze, MWM and Matching/Nonmatching to Position tasks, some effects are delay-dependent

Supplementary tables

Supplementary Table S1. Epidemiological evidence connecting viral and viral-related exposures during pregnancy with offspring risk of ASD or SCZ

★ Exposure timing effect
◆ Exposure type-specific
♣ Extent effect
■ Sex effect
✕ Diagnosis-specific effect
◭ Gene-environment or environment-environment interaction

Reference	Country + birth sample	Exposure type	Disorder	Significant association (Yes/No) & notes	
(Deykin and Macmahon, 1979)	United States, born 3-27 years prior to study for ASD cases	Viral illness (multiple, including ssRNA and dsDNA viruses) in household	ASD	Yes, measles and mumps but not rubella or chickenpox	★◆
(Mednick et al., 1988)	Finland, 1957	Influenza epidemic exposure	SCZ	Yes, second trimester	★
(Kendell and Kemp, 1989)	Finland, 1957	Influenza epidemic exposure	SCZ	No	
(Barr et al., 1990)	Denmark, 1911-1950	Occurrence of influenza infection	SCZ	Yes, second trimester	★
(Sham et al., 1992)	England and Wales, 1970-1979	Influenza epidemic exposure	SCZ	Yes, second trimester	★
(Takei et al., 1993)	England and Wales, 1938-1965	Exposure to periods of time with recorded deaths from influenza	SCZ	Yes, second trimester (5 months before birth)	★
(Takei et al., 1994)	England and Wales, 1938-1965	Influenza outbreak exposure	SCZ	Yes, second trimester	★
(Mednick et al., 1994)	Finland, 1957	Influenza epidemic exposure	SCZ	Yes, second trimester	★
(Selten and Slaets, 1994)	Netherlands, 1957	Influenza epidemic exposure	SCZ	No	
(Susser et al., 1994)	Netherlands, 1957	Influenza epidemic exposure	SCZ	No	
(O'Callaghan et al., 1994)	England and Wales, 1938-1965	Exposure to time with recorded deaths from infectious disease	SCZ	Yes, for bronchopneumonia in 2nd trimester. No for other examined infectious diseases	★◆
(Erlenmeyer-Kimling et al., 1994)	Republic of Croatia, 1957	Influenza epidemic exposure	SCZ	No	
(Kunugi et al., 1995)	Japan, 1957	Influenza epidemic exposure	SCZ	Yes, female-specific effect, second trimester (5 months before birth)	★■
(Takei et al., 1996)	Denmark, 1915-1970	Occurrence of influenza infection	SCZ	Yes, second trimester (4 months before birth)	★
(Morgan et al., 1997)	Australia, 1950-1960	Influenza epidemic exposure	SCZ	Yes for mental retardation no for SCZ. Pnly for exposure in first and second trimesters.	★✕
(Grech et al., 1997)	England and Wales, 1923-1965	Occurrence of influenza infection	SCZ	No effect after adjusting for confounding variables	
(Selten et al., 1998)	Netherlands, 1957	Influenza pandemic exposure	SCZ	No	
(Suvisaari et al., 1999)	Finland, 1951-1969	Occurrence of polio infection	SCZ	Yes, second trimester	★
(Izumoto et al., 1999)	Japan, 1955-1960	Influenza epidemic exposure	SCZ	Yes, second trimester, females	★■
(Westergaard et al., 1999)	Denmark 1968-1988	Influenza prevalence	SCZ	No	
(Brown et al., 2000)	Unted States, 1959-1966,	Occurrence of respiratory infections	SSD	Yes, second but not third trimester	★
(Mino et al., 2000)	Japan, 1957-1965	Influenza epidemic exposure	SCZ	No	
(Brown et al., 2001)	United States, 1963-1965	Rubella pandemic exposure	SCZ	Yes, including associations with behavioural outcomes	

(Buka et al., 2001)	United States, 1960-1966, PDS	Presence of toxoplasma or viral infection markers (IgG) (HSV-1/2, CMV, rubella, parvovirus B19, Chlamydia trachomatis, or human papillomavirus type 16.)	SCZ and other psychotic illnesses	Yes, HSV2 but not other pathogens	♦
(Cahill et al., 2002)	Australia, 1930-1964	Poliovirus epidemic exposure	SCZ , psychosis	No	
(Limosin et al., 2003)	France, 1949-1981	Influenza epidemic exposure	SCZ	Yes, second trimester	★
(Brown et al., 2004b)	Unted States, 1959-1966, PDS	Presence of immune marker (Cytokines)	SCZ	Yes, IL8 in second trimester but not IL1beta, IL6 or Tumor Necrosis Factor (TNF)α	★ ♦
(Brown et al., 2004a)	Unted States, 1959-1966, PDS	Presence of viral (influenza) infection marker (IgG)	SCZ	Yes, first but not second or third trimesters	★
(Brown et al., 2005)	Unted States, 1959-1966, PDS	Presence of toxoplasma infection marker (IgG)	SCZ	Yes, only for high toxoplasma antibody titers, no association for moderate levels	♣
(Babulas et al., 2006)	Unted States, 1959-1966, PDS	Occurrence of genital/reproductive infections	SCZ and SSDs	Yes for periconception (30 days before/after last menstrual period), not for rest of gestation	★
(Brown et al., 2006)	Unted States, 1959-1966, PDS	Presence of viral (HSV-1/2) infection marker (IgG)	SCZ	No (serum collected in third trimester)	★
(Mortensen et al., 2007)	Denmark 1981-1999	Presence of toxoplasma infection marker (IgG)	SCZ related disorders	Yes, upper quartile levels of toxoplasma antibody levels (neonatal blood)	♣
(Byrne et al., 2007)	Denmark 1973-1983	Occurrence of urinary tract and viral (influenza)	SCZ	Yes	
(Buka et al., 2008)	United States, 1959-1965, National Collaborative Perinatal Project (NCPP)	Presence of HSV-2 infection marker (IgG)	Psychosis	Yes, HSV2 and high sexual activity during pregnancy (end of pregnancy serum)	
(Brown et al., 2009a)	Unted States, 1959-1966	Presence of toxoplasma or viral (influenza) infection marker (IgG) or occurrence of respiratory or genital/reproductive infections	SCZ	Yes, association between maternal infection and CSP length in a sample of SCZ patients	
(Sørensen et al., 2009)	Denmark 1959-1961	Occurrence of viral bacterial (sinusitis, tonsillitis, pneumonia, cystitis, pyelonephritis, bacterial venereal infection, and any other bacterial infection)	SCZ	Yes, first but not second trimester after adjusting for confounds	★
(Brown et al., 2009b)	Unted States, 1959-1966	Presence of toxoplasma and viral (influenza) infection marker (IgG)	SCZ	Yes, association between maternal infection and performance on behavioural tasks in SCZ patients	
(Clarke et al., 2009)	Finland 1947-1990	Occurrence of bacterial (pyelonephritis) infection	SCZ	Yes, but only if family history of psychosis	◭
(Ellman et al., 2010)	United States, 1959-1966, drawn from PDS	Presence of Immune marker, Interleukin(IL)-8	SCZ-related MR brain changes	Yes, second/third trimester	★
(Mortensen et al., 2010)	Denmark 1981-1994	Presence of viral (HSV2) infection marker (IgG)	SCZ	Yes (neonatal blood)	
(Atladóttir et al., 2010)	Denmark 1980-2005	Occurrence of viral or bacterial infection (stratified by organ system)	ASD	Yes, viral infection in first trimester and bacterial in second trimester	★ ♦
(Demontis et al., 2011)	Denmark 1975-1981	Presence of viral (HSV-2) marker (IgG, maternal origin)	SCZ gene-environment interaction with NMDA receptors	Yes for gene-environment interaction, but depends on the specific gene and SNP (neonatal blood)	◭

(Brown et al., 2011)	United States, 1959-1966, CHDS	Occurrence of genital/reproductive infections	SCZ and SSDs	Yes, association between maternal infection and behavioural task performance in African-American but not white SCZ cases	
(Goines et al., 2011)	United States, 2000-2001	Presence of immune markers (Cytokines)	Autism and devel. delay	Yes, IFN-γ, IL-4 and IL-5 with ASD, IL-2, IL-4 and IL-6 with developmental disability without ASD, second trimester	
(Hjördis Ósk Atladóttir et al., 2012)	Denmark, 1996-2002	Occurrence of fever and use of sauna	ASD	No for maternal reports of exposure, yes for hospital visits	
(Blomström et al., 2012)	Sweden, 1975-1985	Presence of Toxoplasma and viral (CMV,HSV-1/2) infection markers (antibodies)	SCZ, non affective psychosis	Yes for Toxoplasma and CMV No for HSV1/2 for schizophrenia, no associations with non affective psychosis (neonatal blood)	
(Hjördís Ó Atladóttir et al., 2012)	Denmark 1997-2003	Occurrence of infection (stratified by organ system), fever and antibiotic use	ASD	Yes for influenza infection and prolonged fever with infantile autism, but no for other types of infection investigated	
(Zerbo et al., 2013)	United States, ~1998-2008 (estimated from sample age range)	Occurrence of influenza or fever	ASD and developmental delays	Yes for fever, no for infection	
(Nielsen et al., 2013)	Denmark, 1978-1998	Occurrence of infection (stratified by organ system) or general predisposition to infection	SCZ	Yes, but also for general exposure to infection (not just prenatal infection)	
(Langridge et al., 2013)	Australia, 1984-1999	Occurrence of urinary tract infection (ULI)	ASD and ID	Yes for UTI and ID, but not for UTI and ASD	
(Visser et al., 2013)	Netherlands, ~2000-2006 (estimated from sample age range)	Occurrence of viral/bacterial infections	ASD	Yes. However, for factors other than infection, subtype of ASD altered the association	
(Abdallah et al., 2013)	Denmark (could not access for birth range)	Presence of immune markers (Cytokines)	ASD	Yes, but associations change based on specific cytokine and disease subtypes	
(Mamidala et al., 2013)	India, 2010-2012	Occurrence of infections (stratified by organ system)	ASD	Yes for respiratory but not GI or urinary tract infections	
(Brown et al., 2014)	Finland, 1987-2007	Presenence of immune marker, C-reactive protein (CRP)	autism, SCZ	Yes, 43% difference in risk between highest and lowest CRP quartiles, first and early second trimesters	
(Børglum et al., 2014)	Denmark, born since 1981	Presence of viral (CMV) infection marker (IgG, maternal origin)	SCZ	Yes, association between genotype and CMV, but only for certain SNPs (neonatal blood)	
(Canetta et al., 2014)	Finland, 1983-1988	Presence of immune marker (CRP)	SCZ	Yes, first and early second trimesters	
(Zerbo et al., 2014)	United States, 2000-2001	Immune marker (cytokines and chemokines)	ASD, developmental delay	Yes, but depends cytokines and disorder in question (ASD or developmental disability). Note: most samples did NOT have detectable cytokines (neonatal blood)	
(Betts et al., 2014)	Australia, 1981-1984	Occurrence of vaginal/infection discharge, infant illness susceptibility	Psychosis	Yes for prenatal vaginal infection, association involves infant illness susceptibility	
(Goldstein et al., 2014)	United States, 1959-1966 (NCPP, New England Family Study)	Immune marker (cytokines)	SCZ, affective psychosis (AP)	Yes for IL-6 and TNFα, but associations are gender-specific and not similar for affective psychosis. Third trimester	
(Engman et al., 2015)	Swede, 2005-2008	Presence of CMV infection marker (DNA in dried blood spots)	ASD	Yes, higher rate of congenital CMV in ASD compared to general rate in newborn infants in Sweden (neonatal blood)	
(Fang et al., 2015)	Taiwan, 2000-2007	Occurrence of infection (stratified by organ system) and associated hospital visits	ASD	Yes, third trimester, bacterial infections or >2 visits due to genital infections	
(Blomström et al., 2015)	Sweden 1975-1985	Presence of toxoplasma and viral (CMV,HSV-1/2) infection markers	Non affective psychosis	Yes for Toxoplasma and CMV, but associations depends on levels of acute phase proteins (neonatal blood)	

		(antibodies), as well as acute phase proteins			
(Zerbo et al., 2015)	United States 1995-1999	Occurrence of viral or bacterial infection (stratified by organ system)	ASD	Yes but only for multiple infections or those that required hospitalization	♣
(Sakamoto et al., 2015)	Japan 1994-2003	Presence of CMV infection marker (DNA in dried blood spots)	ASD	Yes, higher rate of congenital CMV in ASD compared to general rate in newborn infants in Nagasaki, Japan (neonatal blood)	
(Lee et al., 2015)	Sweden 1984-2007	Occurrence of inpatient infection diagnosis	ASD/ID	Yes, **does not depend on timing**, potentially higher risk for ASD + ID rather than ASD alone	✖
(Mazina et al., 2015)	Simons Foundation Autism Research Initiative	Occurrence of infection or fever	ASD-related phenotypes	Yes, associations with some behavioural outcomes in ASD but not others, no effect of trimester	
(Cheslack-Postava et al., 2015)	Finland, 1983-1998	Presence of sexually transmitted infection (HSV-2, C. trachomatis) markers (IgG)	SCZ	No, association does not hold after adjusting for covariates, unadjusted values modest, early-mid pregnancy	★
(Canuti et al., 2015)	United States, 1959-1966 (NCPP, New England Family Study)	Presence of viral infection marker (genetic sequence)	SCZ, bipolar	Lower viral prevalence in cases vs controls	
(Koks et al., 2016)	Netherlands, 2002-2006	Presence of immune marker (CRP)	ASD	Yes, only higher levels of CRP, association with behavioural outcome measures in patients, first-second trimester	★ ♣
(Blomström et al., 2016)	Sweden, 1978-1997	Occurrence of viral or bacterial infection	Psychiatric disorders	Yes but only with maternal risk of psychiatric disorders	◭
(Zerbo et al., 2016)	United States, 2000-2003	Presence of immune marker (CRP)	ASD and developmental delays	Yes, lower CRP in ASD mothers, but no associations with developmental disability, mid-pregnancy	★ ✖
(Allswede et al., 2016)	United States, 1959-1966 (NCPP)	Presence of immune markers (cytokines, stratified by subtype - Th1, Th2)	Psychosis	Yes, but association depends on cytokines and their levels (anti-inflammatory Th2, >75th percentile)	◆ ♣
(Nielsen et al., 2016)	Denmark 1977-2002	Occurrence of hospital admissions due to infection	SCZ	Yes, additive but not synergistic effect of infection and anemia	◭
(Konrath et al., 2016)	Austria or Germany	Season of Birth	Schizotypal personality	Yes, late winter and early spring births	★
(Hadjkacem et al., 2016)	Tunisia, 2014	Occurrence of infection (urinary or respiratory)	ASD	Yes for prenatal urinary tract infection and respiratory infection, although postnatal infection more detrimental than prenatal,	
(Brucato et al., 2017)	United States, 1998-2013	Occurrence of genitourinary infection, flu or fever	ASD	Yes for fever but not flu or genitourinary tract infections	◆
(Garofoli et al., 2017)	Italy, 2007-2012	Presence of CMV infection marker (DNA in urine/blood)	ASD	Yes (neonatal blood)	
(Debost et al., 2017)	Denmark 1980-1998	Occurrence of hospital admissions due to infection	SCZ	Yes, only affecting females, but synergistic effect with peripubertal trauma in males	■ ◭
(Zerbo et al., 2017)	United States 2000-2010	Occurrence of viral (influenza) infection and vaccination	ASD	No	
(Jones et al., 2017)	United States, 2000-2003	Presence of immune markers (Cytokines)	ASD/ID, or devel. delay	Yes, although associations exist for specific cytokines and dependent on disease subtypte (ASD +/- intellectual disability), mid-pregnancy	★ ◆ ✖
(Mahic et al., 2017)	Norway, 1999-2008	Presence of toxoplasma or viral (rubella, CMV, HSV-1/2) infection marker (IgG)	ASD	Yes for HSV2 but not toxoplasma, HSV1, rubella, CMV, mid-pregnancy	★ ◆
(Spann et al., 2017)	Finland, 1987-2005	Presence of toxoplasma infection marker (IgG)	ASD	Yes for low but not high levels of maternal toxoplasma antibody	♣
(Gentile et al., 2017)	Italy, ~2002-2013 (estimated)	Presence of CMV infection marker (DNA in blood spots)	ASD	Yes (neonatal blood)	

(Straughen et al., 2017)	United States, 2007-2014	Occurrence of placental inflammation	ASD	Yes, analysis includes specific placental inflammation subtypes (neonatal blood)	♦
(Slawinski et al., 2018)	United States, 2008-2016	Presence of viral (CMV, HSV2) infection markers (IgG)	ASD	Yes, CMV but not HSV2, association with behavioural outcome measures	♦
(Dreier et al., 2018)	Denmark, 1996-2002	Occurrence of infection (stratified by organ system)	Psychosis-like experience age11yr	Yes for fever, genitourinary and influenza, but not for respiratory, **no clear effect of timing** of exposure or symptomatology	♦
(Hornig et al., 2018)	Norway, 1999-2009	Occurrence of fever	ASD	Yes, bigger effect with more fever episodes, second trimester	★ ♣
(Guisso et al., 2018)	Lebanon, subjects age 2-18 (age range unclear, no recruitment timeline)	Occurrence of Viral (influenza, rubella, measles, mumps, CMV, genital herpese) and bacterial (pyelonephritis, lyme disease)	ASD	Yes	
(Christian et al., 2018)	Jamaica, start 2009 for children age 2-8	Occurrence of fever and infection requiring antibiotics	ASD	Yes for maternal fever or infection	
(Mac Giollabhui et al., 2019)	United States, 1959-1966 (CHDS)	Immune markers (Cytokines)	Psychiatric symptoms childhood	Yes, different cytokines associated with different behavioural outcomes	★ ♦
(al-Haddad et al., 2019)	Sweden, 1974-2014	Occurrence of general, severe infection and hospitalization	ASD, BP, Depression	Yes for ASD and depression but not bipolar disorder, not dependent on severity	✖

Supplementary Table S2. Offspring phenotypes after multiple Poly I:C exposures during gestation

Reference	Poly I:C dose/route	Gestational Day	Species	Summary (↑ increase, ↓ decrease, ≈ no change)
(Smith et al., 2012)	5mg/kg i.p.	9.5-13.5 or 13.5-17.5	Mouse	Cortex - MIA-specific ↑cell density in all cortical layers (more in late MIA)
(Fortier et al., 2007)	0.75-1mg/kg i.p. , 0.1mg/kg LPS i.p, turpentine i.m(local inflammation)	10-11 or 15-16 or 18-19	Rat	≈ PPI, ≈ baseline startle
(Malkova et al., 2012)	5mg/kg i.p	10.5+12.5+14.5	Mouse	↓ social preference, ↓ USV calls and duration PND6-14, ↑ grooming, ↑ marble burying, ↓ deposition of scent marks in presence of female urine, ≈ olfactory exploration
(Malkova et al., 2014)	5mg/kg i.p.	10.5+12.5+14.5	Mouse	↑ DOI response in MIA offspring, both behaviourally and molecularly
(Naviaux et al., 2013)	2mg/kg i.p on 12.5 or 3mg/kg on 12.5 and 1.5mg/kg on 17.5	12.5 or 12.5+17.5	Mouse	↓ social preference, ↓latency to fall from rotarod, changes in hypothermia and aerobic metabolism, ≈ PPI ↓ purkinje cells in cerebellar lobule 7
(Pineda et al., 2013)	2.5mg/kg i.p +/- antiIL6, antiIL1B. Also rIL-6, rIL-1B or both	E12-16	Mouse	Altered hippocampal after-discharge, ↓ sociability

(Aavani et al., 2015)	20mg/kg i.p.	12.5-14.5	Mouse	↑ purkinje cell in all cerebellar lobules, age-specific ↑ cerebellar body width, age-specific ↓ sociability (≈ P120, ↓ P40), similar age trend for rotarod behavior
(Oh-Nishi et al., 2010)	4mg/kg i.p.	14.5+16.5 (abortions with 14.5-17.5)	Rat	Hippocampus: ≈ neuron number, altered firing (↓ fiber volley amplitude, ↓ PPF ratio, LTP, synaptophysin in CA1)
(Oh-Nishi et al., 2016)	4mg/kg i.p.	14.5-17.5 daily	Rat	↑Immunoglobulin-kappa-chain
(Ozawa et al., 2006)	5mg/kg i.p.	11.5-16.5	Mouse	≈ Dopamine metabolites or receptors in PFC, ↑ metabolites and ↓ D2R in striatum. ↓ adult PPI ↑ center time in open field and AMPH reaction, ↓ NORT
(Han et al., 2016)	5mg/kg i.p	11.5-16.5	Mouse	Age, region and sub-region-specific alterations in trkB, BDNF and PV (Hippocampus, PFC, Nac). ↓ adult PPI, ≈ locomotion, ↓ NORT
(Han et al., 2017b)	5mg/kg i.p	11.5-16.5	Mouse	↓ BDNF and P-TrkB in PFC. ≈ BDNF or TrkB in NAc or Hippocampus. ≈ locomotion, ↓ NORT
(Han et al., 2017a)	5mg/kg/day i.p	11.5-16.5	Mouse	↑Complement component 1q (C1q) in the PFC. ≈C1q in NAc, or Hippocampus
(Vorhees et al., 2015)	8mg/kg i.p.	14.5-18.5	Rat	Weight gain (WG) and Weight loss (WL) groups based on maternal response to poly I:C. ≈ PPI, ≈ baseline startle, ↑ total distance in WG, ↓ total distance in WL, ↓ MK801 reaction in both WL and WG, ≈ EPM, ≈ marble burying, ↓ MWM
(Ruskin et al., 2017)	5mg/kg	10.5, 12.5 and 14.5	Mouse	↓ male social behavior, ≈ female social behavior, ≈ transmission of food preference. Sex-specific changes in grooming
(Matsuura et al., 2018)	5mg/kg i.p	11.5-16.5	Mouse	≈ juvenile locomotion, ↓ juvenile NORT retention. Region and age-specific changes in expression of PV, Keap1, Nrf2, Sfi1
(Forrest et al., 2012)	10mg/kg i.p.	13.5+15.5+17.5	Rat	Minimal changes in cortical synaptic and Glutamaterigc markers at weaning except some changes in Sox2, synaptobrevin and GluN1
(Okamoto et al., 2018)	0.25U/g on 12.5 and 0.125U/g on 17.5 i.p.	12.5+17.5	Mouse	↓ inhibitory conductance in anterior cingluate and hyperactive layer 2/3 neurons. ↓ sociability
(Lammert et al., 2018)	20mg/kg i.p.	11.5+12.5	Mouse	Strain comparison and relation to intestinal bacteria. ↓ sociability, USVs and ↑ marble burying
(Fujita et al., 2016)	5mg/kg i.p.	11.5-16.5	Mouse	Age and region-specific amino acid/neurotransmitter changes but no age-specific changes in behaviour (no change Open Field, reduced NORT)
(Volk et al., 2015)	20mg/kg i.p.	E11-13 or E15-17	Mouse, Monkey, human tissue	Comparing human, monkey and mice data. Changes due to adult but not prenatal MIA lead to similar phenotype seen in human brains
(Naviaux et al., 2014)	3mg/kg on 12.5 and 1.5mg/kg on 17.5 i.p.	12.5 + 17.5	Mouse	↓ rotarod latency to fall, social approach and Y maze alternations as well as changes in purine metabolism

Supplementary Tables S3. Attempted treatments and preventions in Poly I:C literature

Maternal, genetic and early postnatal interventions

Reference	Gestation Day	Poly I:C Dose and route	Species	Intervention Timing	Intervention name Intervention category	Symptoms treated/prevented
(Song et al., 2011)	8.5	5mg/kg i.v.	Rat	Acute, Maternal, during Poly I:C injection	Anti-inflammatory drug (Nf-kB inhibitor)	PPI, Active Avoidance
(Lipina et al., 2013)	9	2.5 or 5 mg/kg i.v.	Mouse	Acute, Maternal, during Poly I:C injection	Cytokine Antibody: IL6	LI
(Meyer et al., 2008)	9.5	2mg/kg i.v.	Mouse	Genetic	Anti-inflammatory cytokine upregulation: IL10	PPI, Open field, LI
(Vuillermot et al., 2017)	9.5	5mg/kg i.v.	Mouse	Acute, Maternal, during pregnancy	Diet supplementation - Vitamin D	Sociability, Marble burying, fear conditioning
(Luan et al., 2018)	9.5	5mg/kg i.v.	Mouse	Acute, Maternal, during pregnancy	Diet supplementation - Vitamin D	AMPH response
(Smith et al., 2007)	12	20mg/kg i.p.	Mouse	Maternal, during Poly I:C injection	Cytokine Antibody: IL6, IL1beta, IFN-gamma	anti-IL6: Frontal cortex transcriptome, PPI, Open Field, LI, Social Behaviour. Anti-IFN: Open field, LI, Social Behaviour
(Wu et al., 2015)	12.5	20mg/kg i.p.	Mouse	Chronic, Maternal, during pregnancy and until weaning	Diet supplementation - Choline	PPI, Marble burying
(Weiser et al., 2016)	12.5	20mg/kg i.p.	Mouse	Chronic Maternal and postnatal in offspring, prior to pregnancy	Diet - omega-3 (docosahexaenoic acid)	Serum IL-6, Social Behaviour, Grooming
(Coiro et al., 2015)	12.5	20mg/kg i.p.	Mouse	Chronic, Maternal, early postnatal period	Anti-inflammatory drug (ibudilast)	Cortical dendritic spine density/MHCI expression
(Pratt et al., 2013)	12.5	20mg/kg i.p.	Mouse	Genetic	Pro-inflammatory cytokine knockout: IL-6	Fetal chemokines/Cytokines, Basal forebrain ChAT activity
(Pineda et al., 2013)	E12-16	2.5mg/kg i.p.	Mouse	Acute, Maternal, during Poly I:C injection	Cytokine Antibody: IL6, IL1beta	antiIL6: Hippocampal afterdischarge and social behaviour. AntiIL1beta: Hippocampal afterdischarge
(Kim et al., 2017)	12.5	20mg/kg I.p.	Mouse	Acute, Maternal, during Poly I:C injection	Antibiotic (Vancomycin)	Open field, Social Behaviour, USVs, Marble burying
(Lammert et al., 2018)	11.5+12.5	20mg/kg i.p.	Mouse	Acute, Maternal, during Poly I:C injection	Cytokine Antibody: IL17a	Social Behaviour, USVs

Treatment (adult) - Supplementary Table 3. Attempted treatments and preventions in Poly I:C literature

Reference	Gestation Day	Poly I:C Dose and route	Species	Intervention Timing	Intervention name Intervention category	Symptoms treated/prevented
(Shi et al., 2003)	9.5	2.5, 5, 10, 20 mg/kg i.p.	Mouse	Acute	Typical and atypical antipsychotics (Clozapine, Chlorpromazine)	Clozapine and Chlorpromazine: PPI
(MacDowell et al., 2017)	9.5	5mg/kg i.p.	Mouse	Chronic, Adult	Atypical antipsychotic (Paliperidone)	T-maze performance, frontal cortex inflammatory signaling
(Shin Yim et al., 2017)	12.5, 15.5, 18.5	20mg/kg i.p.	Mouse	Acute, Optogenetic	Acute activation and inhibition of distinct cell types	Sociability
(Hsiao et al., 2012)	12.5	20mg/kg i.p.	Mouse	Acute, Adult	Bone Marrow transplant	Open field, Marble burying
(Zuckerman et al., 2003)	14.5	4mg/kg i.v.	Rat	Acute, Adult	Typical and atypical antipsychotics (Haloperidol, Clozapine)	Haloperidol and Clozapine: LI
(Zuckerman and Weiner, 2005)	14.5 (abortions with 16.5)	4mg/kg i.v.	Rat	Acute, Adult	Atypical antipsychotic (Clozapine)	Clozapine: LI
(Klein et al., 2013)	14.5	4mg/kg i.v.	Rat	Acute, Adult	Deep brain stimulation (PFC, dMThalamus and Global Pallidus)	PFC, dMThalamus and Global Pallidus Deep Brain Stimulation: PPI
(Mattei et al., 2014)	15	4mg/kg i.v.	Rat	Chronic, Adult	Antibiotic (Minocycline)	Hippocampal inflammatory signaling/neurogenesis, PPI
(Bikovsky et al., 2016)	14.5	4mg/kg i.v.	Rat	Acute, Adult	Deep brain stimulation (NAc and PFC)	NAc and PFC Deep Brain Stimulation: PPI, LI
(Osborne et al., 2017)	14.5	4mg/kg i.v.	Rat	Chronic, Adult	Cannabidiol	Social interaction, NORT, Y-maze
(Mattei et al., 2017)	14.5	5mg/kg i.p.	Mouse	Chronic, Adult	Antibiotic (Minocycline)	Hippocampal microglial profile and activation, PPI, NORT
(Meyer et al., 2010)	17.5	5mg/kg i.v.	Mouse	Chronic, Adult	Atypical antipsychotic (Clozapine)	MWM
(Malkova et al., 2014)	10.5+12.5 +14.5	5mg/kg i.p.	Mouse	Chronic, Adult	5HT2R Antagonist	DOI response
(Ozawa et al., 2006)	11.5-16.5	5mg/kg i.p.	Mouse	Chronic, Adult	Typical and atypical antipsychotic (Haloperidol, Clozapine)	Clozapine and Haloperidol: NORT
(Naviaux et al., 2014)	12.5 + 17.5	3mg/kg on 12.5 and 1.5mg/kg on 17.5 i.p.	Mouse	Acute, Adult	Anti-purinergic (Suramin)	Social Behaviour, T Maze