Maternal Immune Activation Alters Behavior of Adult Offspring: Sex-Dependent Impairment and Attenuation by Glycan

by

Megan Ann Arnold

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Approved by
Chris Newland, PhD (chair) Department of Psychology
Jeff Katz, PhD Department of Psychology
Chris Correia, PhD Department of Psychology
John Rapp, PhD Department of Psychology
Nick Filipov, PhD Department of Physiology and Pharmacology
Miranda Reed (outside reader), PhD Department of Drug Discovery and Development

Abstract

The developing fetus is exceptionally sensitive to insult. Perturbation during this critical period of development can have lasting effects throughout offspring lifespan. Viral infection and obesity are insults that induce a proinflammatory response in the maternal host and are pertinent to adverse offspring outcomes. Attenuating the maternal inflammatory response, at the time of insult, has shown limited success on fetal outcomes; these factors are necessary for normal fetal development. Attenuating the maternal inflammatory response by increasing anti-inflammatory activity could restore or approximate homeostasis and avoid or attenuate adverse outcomes in offspring. This was tested by inducing maternal immune activation with a high-fat diet or polyinosinic:polycitidylic acid, with some dams receiving concurrent immunomodulatory glycan exposure. Adult offspring were assessed on discrimination reversal tasks and delayed matching to position, measures of behavioral flexibility and working memory, respectively. When differences in behavioral flexibility or working memory did occur, they were often in the opposite direction that was expected. In some instances glycan did attenuate changes to make these animals more similar to controls.

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List of Abbreviations

ASD	Autism Spectrum Disorders
BBB	Blood-Brain Barrier
COX	cyclooxygenase
DOAD	Developmental Origins of Adult Disease
EDS	Extradimensional Shift
FOAD	Fetal Origins of Adult Disease
HFD	High-Fat Diet
IDS	Intradimensional Shift
IFN	Interferon
IL	Interleukin
LNFPIII	Lacto-N-fucopentaose III
MIA	Maternal Immune Activation
NF-κB	Nuclear Factor – kappa-light-chain-enhancer of activated B cells
OD	Original Discrimination
Poly I:C	Polyinosinic:polycytidylic acid
R	Reversal
SDR	Spatial Discrimination Reversal
SFA	Saturated Fatty Acid
Th	T- helper
TLR	Toll-Like Receptor
TNF	Tumor Necrosis Factor

Chapter 1: Introduction

The developing nervous system is highly vulnerable to insult, and disruption of homeostatic development can have lasting effects on offspring long after the insult has ended. Decades of epidemiological and experimental research have implicated prenatal insult with the later development of neurodevelopmental disorders, especially autism spectrum disorders (ASD) and schizophrenia. Based on epidemiological studies, important risk factors for ASD and schizophrenia include maternal: viral or bacterial infection, high-fat diet, diabetes, and/or obesity. In subsequent experimental studies, these risk factors have been shown to play a causal role in changing the trajectory of neural, immune, and behavioral programming in ways that promote outcomes consistent with ASD and schizophrenia in non-human animals.

Although these risk factors may appear unrelated, they all share some degree of maternal immune activation (MIA) (Gilmore & Jarskog, 1997; Sullivan, Nousen, & Chamlou, 2014), meaning the pro- and anti-inflammatory cytokine balance is disrupted. Often, MIA is used to describe disruption that favors a proinflammatory state (Lumeng & Saltiel, 2011; Meyer, Feldon, & Yee, 2009), but it may also refer to the programming of an anti-inflammatory response. The presence of MIA is not always sufficient to produce adverse fetal outcomes – intensity, timing, and duration of the MIA are also important (Gilmore & Jarskog, 1997; Meyer et al., 2006). Maternal immune activation that produces an abnormal immune response in offspring is especially pertinent to neurodevelopmental disorder research. Specifically, greater baseline inflammation and sensitized proinflammatory immune response to proinflammatory stimuli following MIA. This characteristic abnormal immune response in offspring following MIA has been associated with generally poorer cognitive performance (Crichton et al., 2011; Rajia, Chen, & Morris, 2010), ASD (Dodds et al., 2011; Krakowiak et al., 2012; Lyall, Munger, O'Reilly,

Santangelo, & Ascherio, 2013; Van Lieshout, Taylor, & Boyle, 2011), and schizophrenia (Knuesel et al., 2014; Yolken & Torrey, 1995). Importantly, this abnormal immune response is not readily apparent at birth. Instead, these effects of MIA are unmasked following some later insult or stress, which may account for the delay in symptom onset for some neurodevelopmental disorders (Meyer & Feldon, 2010; Bilbo & Tsang, 2010; Knuesel et al., 2014).

To date, there has been limited success with interventions that attenuate the maternal proinflammatory response. Cytokines, including proinflammatory cytokines, are necessary for normal fetal development (Bilbo & Schwarz, 2012; Boulanger, 2009; Deverman & Patterson, 2009; Garay & McAllister, 2010; Stolp, 2013). Attenuating the proinflammatory response during development can also produce adverse fetal outcomes (Meyer, Schwarz, & Müller, 2011). Meyer, Schwarz, et al. (2011) offer an interesting solution to this logistical issue. They propose that the key to adverse developmental programming by maternal immune activation is the disruption of proinflammatory and anti-inflammatory cytokine balance and restoring this balance would prevent adverse effects. This balance could be achieved by increasing anti-inflammatory activity instead of reducing proinflammatory activity. Although levels of proinflammatory cytokines would still be elevated, the increased anti-inflammatory cytokine levels would theoretically result in a restoration of homeostatic cytokine balance possibly preventing adverse developmental programming.

This type of intervention could prove useful for preventing or attenuating symptoms of neurodevelopmental disorders that are associated with increased maternal proinflammatory response in gestation. The subsequent sections will review developmental programming in general, as well as, the specific role maternal immune activation plays in the developmental programming of neurological and behavioral outcomes in offspring. This review will separately

focus on acute inflammation characteristic of a viral immune response and chronic inflammation characteristic of low-grade inflammation as a result of consuming a diet high in saturated fatty acids. The subsequent sections are a review of epidemiological evidence linking these two patterns of maternal immune activation to incidence and symptoms (neurological and behavioral) of ASD and schizophrenia. Finally, the review will address a potential intervention, immunomodulatory glycan, to prevent or attenuate these adverse neurological and behavioral outcomes.

Inflammation and Developmental Programming

Developmental programming (Barker, 1997) refers to a process by which an adverse fetal environment, especially during critical periods of fetal development, permanently change immune, neural, and/or endocrine function (Bilbo & Schwarz, 2009; Lucas, 1994). These changes in turn promote diseased or disordered states in the offspring that can appear well into adulthood or even aging. This hypothesis is often referred to as the fetal origins of adult disease (FOAD) hypothesis (Barker, 1995). Given that not all critical periods of development occur *in utero*, this hypothesis can be expanded to include any critical period of development and is known as the Developmental Origins of Adult Disease (DOAD) hypothesis (Barker, 2003). Interestingly, the alterations programmed by the adverse environment promote fetal survival in the short-term (Barker, 1997), but they later produce adverse health outcomes when the postnatal environment does not match that in development (Gluckman, Hanson, & Spencer, 2005; Tamashiro & Moran, 2010). For example, severe fetal undernutrition programs insulin resistance in offspring (Phillips & Barker, 1997). Under starvation conditions insulin resistance is consistent with survival because it promotes adiposity, but when calories are abundant it promotes obesity, type II diabetes, and metabolic syndrome (Gluckman et al., 2005).

Although *developmental programming* was conceived as a way to understand the relationship between fetal undernutrition with offspring obesity and related health outcomes (De Boo & Harding, 2006; Hales & Barker, 2001; Phillips & Barker, 1997), this paradigm has also proven useful for understanding non-nutritional programming and its role in long-term offspring health and potential origins of some neurodevelopmental disorders including ASD and schizophrenia. This approach has been particularly useful for studying these disorders because of their epidemiologically identified risk-factors (Buka et al., 2001; Dodds et al., 2011; Knuesel et al., 2014; Krakowiak et al., 2012; Lyall et al., 2013; Van Lieshout et al., 2011; Yolken & Torrey, 1995); hypothesized neuro-immune developmental programming (Gilmore & Jarskog, 1997; King & Lord, 2011; Meyer, Feldon, & Dammann, 2011); and altered immune (Ashwood et al., 2011a, 2011b; Müller & Schwarz, 2010; Nawa & Takei, 2006), neural (Fatemi, 2008), and behavioral function (E. L. Hill, 2004; Lord, Cook, & Leventhal, 2000; Meyer, Feldon, et al., 2011). Of their overlapping impairments, a behaviorally rigid endophenotype and working memory deficits are particularly worthwhile for investigation: behavioral flexibility, the inverse of rigidity, is by definition necessary for learning to occur (Neuringer, 2002) and deficits in this behavioral domain are well established in both ASD and schizophrenia (King & Lord, 2011; Leekam *et al*. 2011; Zeina *et al*. 2014; Hill, 2004; Rodriguez & Thompson, 2015; Jazbek *et al*. 2007; Pantelis *et al*. 2009). The latter, working memory, is necessary for a stimulus(i) to occasion behavior in its absence (Goldman-Rakic, 1994; Lind, Enquist, & Ghirlanda, 2015; K. G. White & McKenzie, 1982), however, working memory deficits are well-established in schizophrenia (Dudchenko, Talpos, Young, & Baxter, 2013), but less consistently observed in ASD (Barendse et al., 2013; Chien et al., 2015; Sinzig, Morsch, Bruning, Schmidt, & Lehmkuhl, 2008; Steele *et al*. 2007).

The developing nervous system is especially vulnerable to proinflammatory developmental programming by MIA because neither the placenta nor the (as-yet developed) blood-brain barrier (BBB) confer absolute protection from the maternal immune system (Bilbo, 2011; Bolton & Bilbo, 2014; Hsiao & Patterson, 2011; Urakubo, Jarskog, Lieberman, & Gilmore, 2001). Barrier permeability to immune factors is important because cytokines are necessary for normal placental (Bilbo, 2011) and offspring development (Bilbo & Schwarz, 2012; Boulanger, 2009; Deverman & Patterson, 2009; Garay & McAllister, 2010; Stolp, 2013). In addition to altering the course of neurodevelopment, there is also evidence that MIA can permanently program an abnormal immune response in offspring that matches the maternal immune response during development, which is referred to as *immune priming* (Bilbo & Tsang, 2010; Knuesel et al., 2014). Furthermore, the typically developed BBB remains permeable to immune factors (Degos et al., 2010), like cytokines which are involved in normal neural and behavioral processes (Deverman & Patterson, 2009; Vitkovic, Bockaert, & Jacque, 2000). This permeability renders the nervous system especially vulnerable to disruption by immune priming. Any event that causes a deviation from the normal ebb and flow of cytokines during pregnancy can permanently alter the trajectory of offspring neural development and immune response to subsequent challenge (Albensi & Mattson, 2000; Hagberg, Gressens, & Mallard, 2012).

Immune priming and subsequent neural and behavioral disruption is especially relevant to individuals with genetic predisposition for neurodevelopmental disorders because these individuals may be especially sensitive to these changes (A. S. Brown, 2011; Ehninger et al., 2010; Machon, Mednick, & Schulsinger, 1983; Meyer, Feldon, & Yee, 2009; Nawa & Takei, 2006). Patients with ASD and schizophrenia showed elevated basal serum levels of proinflammatory cytokines relative to age-matched controls even in the absence of immune

challenge suggesting a preferentially proinflammatory state in these individuals (Al-Hakeim, Al-Rammahi, & Al-Dujaili, 2015; Ashwood et al., 2011a, 2011b; Choi et al., 2016; Malik et al., 2011). Meaning, proinflammatory pathways are in a constant state of activation, even in the absence of an immune challenge.

The way MIA interacts with genetic predisposition could also account for delayed symptom onset in schizophrenia (Ellman, Yolken, Buka, Torrey, & Cannon, 2009; Knuesel et al., 2014), while symptoms of ASD are established much earlier in life (Arndt, Stodgell, & Rodier, 2005; Lord, Risi, et al., 2000). Meyer, Feldon, et al. (2011) have hypothesized that MIA programming of persistent postnatal inflammation in offspring will give rise to ASD. In contrast MIA programming of latent immune priming that is unmasked during some later life stage, like adolescence, may account for delayed symptom onset in disorders like schizophrenia (Kinney et al., 2010; Meyer, 2013; Meyer, Feldon, et al., 2011; Meyer, Feldon, & Yee, 2009; Spear, 2000).

Given the evidence indicating MIA-induced cytokine imbalance is critical for neurodevelopmental disorders, interventions that attenuate this activation are appealing (Harry & Kraft, 2012). Preventing or attenuating MIA could be useful for ameliorating or dampening adverse postnatal outcomes for offspring. As appealing as these interventions may be, restoring cytokine balance during gestation has proven to be a delicate matter. Immune factors play a critical role in normal offspring development (Bilbo & Schwarz, 2012; Harry & Kraft, 2012; Huh et al., 2000; Nakanishi et al., 2007; Schafer et al., 2012; Stellwagen & Malenka, 2006; Wang, Wu, Shieh, & Wen, 2002), but homeostatic levels of these factors, especially the cytokines, change throughout non-clinical pregnancy (Mor & Cardenas, 2010). To further complicate the matter, insufficient levels of these immune factors can also produce abnormal and behavioral function in offspring (Meyer, Feldon, et al., 2011). Therefore, appropriately

attenuating proinflammatory pathways, without overly reducing cytokine levels and thus impairing normal development, would be an exceedingly difficult intervention to implement. To avoid such difficulties it may be possible to restore homeostasis not by decreasing proinflammatory activity, but by increasing anti-inflammatory activity (Meyer, Feldon, & Yee, 2009).

Modeling MIA

Establishing causal relationships between prenatal factors, like MIA, and offspring behavioral impairment requires the development and use of experimental, usually rodent, models. In general, the severity and pattern of MIA modeled in these experiments fall into one of two categories: moderate, acute activation during critical windows of fetal development or low-grade, chronic activation. There is a staggering number of stimuli that induce acute immune activation, but here only models of viral infection will only be reviewed as viral mimic interventions were used in the inflammation experiment. In the following section, review of chronic inflammation will focus on maternal obesity and diet, specifically one high in saturated fatty acids.

Viral Infection and Acute Inflammation: Neurobiological Consequences

There is extensive epidemiological evidence suggesting that maternal influenza infection is a particularly potent risk factor for both ASD and schizophrenia (Meyer, 2014; Patterson, 2011, 2012). Some experimental models have focused on directly infecting pregnant dams with virus (Meyer & Feldon, 2010; Meyer, Feldon, & Fatemi, 2009). These models of infection allow for precise control of when the insult occurs in gestation. Control over the timing of insult is imperative for determining periods of maximum offspring neural, immune, and behavioral vulnerability in offspring and whether these vulnerabilities are consistent with

neurodevelopmental disorders in humans (Meyer, Feldon, & Fatemi, 2009). Despite its ecological validity, subsequent research in this area has made quite clear that influenza *itself* is not responsible for adverse fetal outcomes because the virus was not detected in fetal tissues (Fatemi et al., 2012; Shi, Tu, & Patterson, 2005). Instead, influenza-induced MIA, not the virus itself, is the key factor linking infection and proinflammatory developmental programming in offspring (Buka et al., 2001; Gilmore & Jarskog, 1997; Patterson, 2009; B. D. Pearce, 2001).

Polyriboinosinic:polyribocytidylic (Poly I:C) acid is a synthetic analog of double-stranded RNA and a potent toll-like receptor (TLR)-3 agonist (Alexopoulou, Holt, Medzhitov, & Flavell, 2001) that induces an immune response mimicking viral infection (Cunningham, Campion, Teeling, Felton, & Perry, 2007; Field, Campion, Warren, Murray, & Cunningham, 2010; M.-E. Fortier et al., 2004). TLR-3 receptors are located intracellularly, meaning Poly I:C is capable of not only crossing the lipid bilayer of cells, but also the placental barrier (Marshall-Clarke *et al*., 2007; Koga & Mor, 2008). In rodents, immediate, overt symptoms of Poly I:C include a febrile episode and sickness behaviors (M.-E. Fortier et al., 2004). At the cellular level, Poly I:C activates the TLR-3 pathway, which causes the production of anti-viral interferons, proinflammatory cytokines via NF-κB- and activator protien-1- dependent mechanisms, and cell death (Alexopoulou et al., 2001; Field et al., 2010; Reisinger et al., 2015).

Exposure to Poly I:C during pregnancy produces a characteristic immune profile quite similar to that observed in non-pregnant animals: shortly after Poly I:C injection of dams, there is an increase in the expression of mRNA for the cytokines interleukin (IL)-2, IL-5, IL-6, TNF-α, IL-1β, interferon (IFN)-β, and cyclooxygenase (COX)-2 (Arsenault, St-Amour, Cisbani, Rousseau, & Cicchetti, 2014; Cunningham et al., 2007; M.-È. Fortier et al., 2004; Gilmore, Jarskog, & Vadlamudi, 2005; Meyer, Murray, et al., 2008; Meyer et al., 2006). These Poly I:C

induced changes are rapid with peak immune response occurring within hours of injection (M.-È. Fortier et al., 2004). Although the immune response is rapid, it is fleeting – TNF-α levels normalize within 24h of injection (Gilmore et al., 2005).

Importantly, repeated postnatal dosing with Poly I:C that is separated by one to three weeks, does not quantitatively or qualitatively alter the immune response between exposures (Cunningham et al., 2007). This fleeting immune response is advantageous because the precise control over the timing of insult and the lack of blunted response to repeated Poly I:C administration allows for repeated testing within the same animal. That being said, developmental exposure to Poly I:C has been shown to program an abnormal immune response in offspring, specifically one that favors a proinflammatory state (Garay, Hsiao, Patterson, & McAllister, 2013; Giulivi, Napoli, Schwartzer, Careaga, & Ashwood, 2013; Han, Li, Meng, Shao, & Wang, 2011; Kranjac et al., 2012; Meyer, Feldon, Schedlowski, & Yee, 2005; Meyer, Nyffeler, Schwendener, et al., 2008; Rose et al., 2017).

Together, these findings highlight key methodological advantages of inducing MIA with Poly I:C instead of direct infection with a live virus. Using viral infection can produce inconsistency in the degree and duration of MIA, especially when comparing across infectious agents (Boksa, 2010) whereas with Poly I:C the dosing is consistent, the inflammation is constant, and the degree of inflammation can be determined by the dose, giving the investigator more control and reducing variability. Findings from Poly I:C can be generalized to any virus that produces double-stranded RNA during replication. Furthermore, influenza models do not allow for the control of maternal antibodies and subsequent offspring autoimmunity (Müller & Schwarz, 2010; Wright & Murray, 1993), while Poly I:C avoids a blunted immune response following repeated administrations. This is a critical advantage because an abnormally

heightened immune response in MIA is a major component of hypotheses describing the etiology of disorders thought to involve immune priming (Meyer, Feldon, et al., 2011). Testing these hypotheses inherently requires exposing offspring to the proinflammatory agent multiple times.

Viral Infection and Acute Inflammation: Behavioral Consequences

In addition to these methodological advantages, deficits observed in offspring prenatally exposed to Poly I:C recapitulate many deficits observed in influenza models. Some important deficits, because of their relevance to behavioral flexibility, include impaired intradimensional shifting (IDS) and extradimensional shifting (EDS) (Canetta et al., 2016; Choi et al., 2016; Han et al., 2011; Malkova, Yu, Hsiao, Moore, & Patterson, 2012; Meyer et al., 2005, 2006; Rose et al., 2017; Wallace, Marston, McQuade, & Gartside, 2014; Z. Zhang & van Praag, 2015) and sensorimotor gating (Meyer, Nyffeler, Yee, Knuesel, & Feldon, 2008). Both of these behavioral impairments are consistent with neural abnormalities also observed in Poly I:C offspring including: frontal cortex (Garay et al., 2013; Gilmore, Fredrik Jarskog, Vadlamudi, & Lauder, 2004; Nyffeler, Meyer, Yee, Feldon, & Knuesel, 2006; Y. Zhang, Cazakoff, Thai, & Howland, 2012) and dopaminergic dysfunction (Luchicchi et al., 2016; Meyer et al., 2005; Meyer, Nyffeler, Yee, et al., 2008; Ozawa et al., 2006).

Poly I:C offspring also showed impaired behavioral flexibility, but they did not show impaired acquisition of the spatial discrimination, which is interesting because mesolimbic region dysfunction has been noted in Poly I:C offspring (Nyffeler et al., 2006; Ozawa et al., 2006; Zuckerman, Rehavi, Nachman, & Weiner, 2003). Interestingly, these findings are consistent with behavioral outcomes in ASD (Yerys et al., 2009) and schizophrenia (Pantelis et al., 2009). Furthermore, Poly I:C offspring showed impaired spatial matching to position, which

is a measure of working memory (Meyer & Feldon, 2009; Richetto, Calabrese, Meyer, & Riva, 2013).

Although infecting animals with influenza recapitulates changes observed in epidemiological studies of human offspring, influenza itself is not responsible for these outcomes. Viral mimic models, like Poly I:C, have been critical for identifying the importance of MIA the mechanism that unifies may seemingly disparate infection-based risk factors. More generally, these models have been integral in understanding developmental programming of latent adverse offspring outcomes, like immune priming. This understanding may be critical for identifying the etiology of specific neurodevelopmental disorders and disordered behavior more generally as well as a time period during and mechanism by which to intervene (Meyer, Schwarz, et al., 2011).

Obesity and Chronic Inflammation: Neurobiological Consequences.

Obesity is a major risk factor for a variety of adverse health outcomes including metabolic syndrome (Cottrell & Ozanne, 2008), type II diabetes (Armitage, Taylor, & Poston, 2005), high blood pressure and cardiovascular disease (Schulz, 2010), and cognitive impairments (Hargrave, Jones, & Davidson, 2016). Adipose is an endocrine organ that secretes proinflammatory factors – leptin, C-reactive protein, tumor necrosis factor (TNF)-α, IL-1β, and IL-6 – and anti-inflammatory factors: – adiponectin, resistin, and IL-10 (Das, 2001; Hariri & Thibault, 2010; Parimisetty et al., 2016). Under non-clinical circumstances, levels of proinflammatory and anti-inflammatory factors secreted from adipose in the periphery are balanced. As excess adipose accumulates this peripheral balance tips in favor of a proinflammatory state (Parimisetty et al., 2016). Indeed, humans with obesity show elevated peripheral levels of proinflammatory biomarkers and decreased levels of anti-inflammatory

markers compared to non-obese individuals (Spyridaki, Avgoustinaki, & Margioris, 2016). Due to this peripheral inflammation, obesity has been described as a state of low-grade, chronic inflammation (Das, 2001). Inflammation in peripheral tissues is important because it promotes the development of metabolic disorders (Armitage et al., 2005; Crichton et al., 2011; Everard & Cani, 2013; Gniuli et al., 2008; Whitaker, Totoki, & Reyes, 2012), increases BBB permeability thus promoting neuroinflammation (Buckman et al., 2014; Heneka & Nicotera, 2016; Pepping, Freeman, Gupta, Keller, & Bruce-Keller, 2013; Stolp et al., 2011), and is associated with cognitive dysfunction (Marqués-Iturria et al., 2013; Miller & Spencer, 2014; Pepping et al., 2013) including impaired EDS (Lasselin et al., 2016) and delayed recall (Coppin, Nolan-Poupart, Jones-Gotman, & Small, 2014; Cournot et al., 2006; Nguyen, Killcross, & Jenkins, 2014).

Maternal obesity and corresponding low-grade, chronic inflammation not only adversely affects maternal health, but can also result in adverse developmental programming of offspring (Alfaradhi & Ozanne, 2011; Bilbo & Tsang, 2010; Cottrell & Ozanne, 2008; Hargrave et al., 2016; Nivoit et al., 2009; Vucetic, Kimmel, Totoki, Hollenbeck, & Reyes, 2010). In brief, maternal obesity has been shown to increase the risk of offspring obesity and associated adverse health outcomes (Elahi et al., 2009; Samuelsson et al., 2008; Yu et al., 2011), inflammation (Kang, Kurti, Fair, & Fryer, 2014), and cognitive impairment (Davidson et al., 2013; Gillette-Guyonnet et al., 2007; Y. Lee et al., 2010).

Increased risk of obesity is important because of its relation to metabolic and cardiovascular disorders (Armitage et al., 2005; Cottrell & Ozanne, 2008; Schulz, 2010), which are indirectly albeit importantly relevant to neural and behavioral outcomes. Metabolic alterations can affect motivating operations of food-reinforcement (Grissom et al., 2014; X. Zhang et al., 2008), alter feeding (Niswender & Schwartz, 2003; Sample, Martin, Jones,

Hargrave, & Davidson, 2015; Sun et al., 2012), increase the palatability of obesogenic foods (DelParigi, Chen, Salbe, Reiman, & Tataranni, 2005; Figlewicz & Benoit, 2009), and contribute to postnatal low-grade, chronic inflammation in offspring (Bilbo & Tsang, 2010). Together, low-grade chronic MIA-induced programming and promotion of continued inflammatory insult are important for understanding relationships between maternal obesity, general cognitive delay (Hinkle et al., 2012), and increased risk of some neurodevelopmental disorders (Dodds et al., 2011; Khandaker, Dibben, & Jones, 2012; Krakowiak et al., 2012; Van Lieshout et al., 2011) in offspring.

Diet-induced obesity has become the preferred manner by which to model maternal obesity and offspring outcomes for four important reasons. First, there is little evidence for a genetic contribution to the etiology of obesity in humans (J. O. Hill & Peters, 1998). Instead, the combination of diet, sedentary lifestyle, and developmental programming better accounts for the increase in obesity for all ages in countries like the United States (Dyer & Rosenfeld, 2011; Ogden, Carroll, Fryar, & Flegal, 2015). Second, dietary models capture the slow onset of obesity and associated pathologies and behavioral perturbation better than genetically modified rodents (Everard et al., 2011; Fulton et al., 2006; Stranahan, Hao, Dey, Yu, & Baban, 2016; Winocur et al., 2005). That said, the importance of genetically modified rodents should not be discounted because they remain useful for understanding the role specific factors play in developmental programming, organ system dysfunction, and behavioral perturbation. Third, diet-induced obesity models allow for the comparison of diets that differ in percent kcal macronutrient profiles on physiological and behavioral outcomes. Fourth, dietary exposure affects breast milk quality, meaning insult may continue through weaning (Franco et al., 2012; Saste et al., 1998; Sun et al., 2012; C. L. White, Purpera, & Morrison, 2009).

For dietary models, dams are typically exposed to an obesogenic diet for several days to weeks prior to mating with an (often) unexposed sire. Starting the dietary exposure prior to mating is important because it allows sufficient time for metabolic and inflammatory changes to occur. Dietary exposure can continue through gestation and lactation or cross-fostering studies can be used to identify critical periods of development (Williams, Seki, Vuguin, & Charron, 2014). A high-fat diet is often used as an obesogenic diet in animal models because it resembles a diet common in countries with high rates of obesity. The percent kcal macronutrient profile of a HFD consists of 20% protein, 35-20% carbohydrate, and 45-60% fat (Guillemot-Legris & Muccioli, 2017). This is in contrast to a standard rodent chow diet with a percent kcal macronutrient profile of 15% protein, 75% carbohydrate, and 10% fat (Guillemot-Legris & Muccioli, 2017). That said, the specific fatty acid profile will determine whether a diet high in fat is beneficial or adverse – all other macronutrients being equal (Winocur & Greenwood, 1999).

In general, diets high in monounsaturated fatty acids, like olive oil or avocado, or polyunsaturated fatty acids with a high ω-3:ω-6 ratio, like salmon, are not only protective against obesity (Cintra et al., 2012) and adverse offspring outcomes (Camer et al., 2015), but have been shown to attenuate obesity- or diet-induced inflammation (Cintra et al., 2012; Song, 2004; Song, Leonard, & Horrobin, 2004). Contrarily, diets high in saturated-fatty acids, like lard; diets high in trans-unsaturated fatty acids, like palm oil; or diets with a low ω-3:ω-6 ratio generally produce adverse health outcomes (Armitage et al., 2005; Buckley et al., 2005; Greenwood & Winocur, 1996; Lyall et al., 2013). Specifically, diets high in saturated or trans-unsaturated fatty acids increased adiposity (Akagiri et al., 2008), induced metabolic syndrome (Buckley et al., 2005; Srinivasan, Katewa, Palaniyappan, Pandya, & Patel, 2006), increased peripheral (Cani et al.,

2007; Lumeng & Saltiel, 2011) and central inflammation (Cintra et al., 2012; Elahy et al., 2015; Manousopoulou et al., 2015; Nerurkar et al., 2011) which primed the immune system to subsequent insult (Bilbo & Tsang, 2010; C. L. White, Pistell, et al., 2009), and impaired learning and memory (Kanoski, Meisel, Mullins, & Davidson, 2007; Lu et al., 2011). These diets may also be involved in the etiology of neurodevelopmental disorders – the offspring of women who consumed diets very low in ω-3 had a 34% increased risk of ASD (Lyall et al., 2013).

Extended exposure to a diet rich in saturated-fatty acids not only promotes the development of obesity and metabolic dysfunction, but also changes to the inflammatory profile can occur mere days after dietary exposure weeks before the onset of obesity or metabolic dysfunction (Münzberg, Björnholm, Bates, & Myers, 2005; Thaler et al., 2011; Williams et al., 2014). This is important because it suggests a proinflammatory state is not only important for adverse health progression, but it also provides a rapid and therefore appealing way to induce chronic, low-grade inflammation relevant to developmental programming in offspring (Ashino et al., 2012; Volpato et al., 2012). Maternal consumption of a saturated-fatty acid rich diet produced low-grade, chronic maternal immune activation and offspring showed evidence of immune priming: increased basal microglial activation (Kang et al., 2014), increased microglial response following immune challenge in adult offspring (Bilbo & Tsang, 2010; C. L. White, Pistell, et al., 2009), and elevated basal levels of proinflammatory cytokines like IL-1β and TNF-α (Ashino et al., 2012; Kang et al., 2014; C. L. White, Pistell, et al., 2009).

An important limitation of dietary models is the difficulty separating developmental effects of diet from obesity itself because extended feeding of an obesogenic diet, like one high in saturated-fatty acids, will eventually result in obesity (Hariri & Thibault, 2010). Few studies have separated out these two effects by exposing animals to isocaloric, or near isocaloric

standard laboratory chow diet or a saturated-fatty acid rich diet (Franco et al., 2012; Hao, Dey, Yu, & Stranahan, 2016; Raygada, Cho, & Hilakivi-Clarke, 1998). When compared, a saturated-fatty acid rich diet clearly induces greater inflammation than standard chow (Hao et al., 2016; C. L. White, Pistell, et al., 2009), but there is less consistent evidence for developmental programming of offspring in the absence of obesity (C. L. White, Purpera, et al., 2009).

Obesity and Chronic Inflammation: Behavioral Consequences. Despite this caveat, developmental programming by maternal consumption of a diet rich in saturated-fatty acids often produces deficits that are in-line with obesity models. Some important deficits because of their relevance to behavioral flexibility include altered motivational operations of food-reinforced behavior (Naef et al., 2008), impaired acquisition of spatial discriminations (Bilbo & Tsang, 2010; Tozuka et al., 2010), and possibly deficits in reversal learning (Wu et al., 2013; Menting *et al*. 2019), and working memory (Cordner & Tamashiro, 2015). These findings are consistent with evidence from human obesity studies (Lasselin et al., 2016).

Offspring of dams consuming a saturated-fatty acid rich diet in gestation show increased preference for obesogenic foods high in fat, sugar, and salt (Ong & Muhlhausler, 2011; Sullivan, Smith, & Grove, 2011; Vucetic & Reyes, 2010). Additionally, these offspring also showed abnormal dopamine, opioid, and GABA function in the nucleus accumbens (Grissom et al., 2014; Naef et al., 2011; Vucetic et al., 2010), ventral tegmental area (Alfaradhi & Ozanne, 2011; Naef et al., 2008), and prefrontal cortex (Vucetic & Reyes, 2010). Each of these neurotransmitter systems and brain regions play important roles in food-based reinforcement, liking, wanting, and learning (Berridge, 1996; Kelley, 2004; Vucetic & Reyes, 2010; Woolley, Lee, & Fields, 2006). Altered food preference could be one mechanism by which maternal diet promotes adverse offspring outcomes in humans because the preferred foods are those that

promote obesity and inflammation. From a procedural perspective, these changes are important because sucrose is often used as a reinforcer in experiments.

Despite the evidence of improved reinforcer efficacy of palatable food, there is clear evidence for impaired acquisition of spatial discriminations in offspring gestationally exposed to a diet rich in saturated-fatty acids (Bilbo & Tsang, 2010; Lu et al., 2011; Molteni, Barnard, Ying, Roberts, & Gómez-Pinilla, 2002; Page, Jones, & Anday, 2014; Pini, do Vales, Braga Costa, & Almeida, 2016; Robb et al., 2017; Sullivan et al., 2014; Tozuka et al., 2010). Impaired spatial discrimination learning is consistent with dysfunction in the aforementioned brain regions – in particular striatal dysfunction has been shown to be related to impaired spatial discrimination (Bussey, Muir, Everitt, & Robbins, 1996; Owen et al., 1992). In addition to spatial learning, impaired acquisition of fixed-ratio schedules have also been observed in offspring gestationally exposed to a diet rich in saturated-fatty acids (Rodriguez et al., 2012).

Abnormal neurodevelopment of and increased neuroinflammation in these cortical regions are likely to have important implications for executive function including intradimensional and extradimensional set-shifting in behavioral flexibility. Despite its importance, few studies have assessed this aspect of behavior following gestational exposure to a saturated-fatty acid rich diet. In one study, male offspring gestationally exposed to a saturated-fatty acid rich diet performed more perseverative errors following an intradimensional shift than standard laboratory chow offspring (Wu et al., 2013). In another study, females gestationally exposed to a diet rich in saturated fatty acids showed impaired working memory on a 5-choice serial reaction timed task, specifically these mice required longer stimulus durations to perform the correct response (Mckee, Grissom, Herdt, & Reyes, 2017).

Importantly, there is a wealth of evidence demonstrating impaired spatial learning and memory in offspring gestationally exposed to saturated-fatty acid rich diet (Lu et al., 2011; Page et al., 2014; Robb et al., 2017; C. L. White, Pistell, et al., 2009; Winocur & Greenwood, 2005). Within the hippocampus of these offspring, altered apoptosis, differentiation, neurogenesis, and synaptic plasticity (Robb et al., 2017) has been observed. The dentate gyrus seems especially vulnerable to this perturbation (Niculescu & Lupu, 2009; Page et al., 2014; Tozuka et al., 2010). Interestingly, insulin resistance, which is an important aspect of metabolic syndrome, may also be relevant to impaired memory in these studies – insulin's normal function in the hippocampus is important for spatial memory (McNay et al., 2010). This abnormal proliferation and apoptosis, is not limited to the hippocampus but has also been observed in the cortex (Manousopoulou et al., 2015; Niculescu & Lupu, 2009).

Together, deficits in spatial and schedule learning may reflect a global dysfunction in reinforcement, perhaps as a consequence of the previously outlined neurotransmitter systems. To date, there have been no assessments of extradimensional set-shifting following developmental programming by maternal diet rich in saturated-fatty acids. Such a study would complement the literature assessing the role maternal immune activation plays in offspring developmental programming of cognitive dysfunction and neurodevelopmental disorder risk.

Measuring Behavioral Flexibility

Behavioral flexibility is a fundamental component of behavior change (Neuringer, 2004; Skinner, 1953, 1981) and describes the ability to modify behavior in response to changing environmental contingencies, an important aspect of executive function (V. J. Brown & Bowman, 2002). For humans, this aspect of executive function is often assessed with the intra-extra-dimensional set shift subtest of the Cambridge Neuropsychological Test Automated

Battery (CANTAB) (Owen, Roberts, Polkey, Sahakian, & Robbins, 1991; Robbins, 1996; Sahakian & Owen, 1992) or the Wisconsin Card Sorting Test (WCST). Performance on the intradimensional shift (IDS) can be characteristic of specific neural dysfunction (Ragozzino, 2007) and neuropsychiatic disorders (Pantelis et al., 1999; Russo et al., 2007).

The focus of this review will be on the CANTAB because it is comprehensive and relevant to the animal literature. For the CANTAB task, participants must first acquire an original discrimination (OD) along some perceptual dimension – for example choosing purple, not blue, stimuli would result in reinforcement. Inability or difficulty acquiring the OD because of excessive errors has been observed in patients with striatal dysfunction due to Parkinson's disease (Owen et al., 1992) and animals with posterior cingulate lesions (Bussey et al., 1996). Patients with schizophrenia predominated by negative and cognitive symptoms required more trials to master the OD than patients with frontal lobe damage or matched controls (Pantelis et al., 1999). This delay in OD mastery was not due to increased errors, but to increased omissions or failure to respond during the trial. Excessive omissions could be due to anhedonia, which is consistent with this subtype of schizophrenia (Berridge, 1996).

Following acquisition of the OD, an intra-dimensional shift (IDS) occurs. That is, the contingency reverses along the same perceptual dimension as the OD (Owen et al., 1991). Now, choosing blue, not purple, stimuli produces reinforcement. As with the OD, inability or difficulty acquiring the IDS is indicative of specific neurological function and certain neuropsychiatric disorders. Often, impaired acquisition of the IDS is due to perseverative responding in which the increase in errors following the reversal persists for a longer period than in control/comparison groups (Dalley, Cardinal, & Robbins, 2004). Dysfunction and serotonin depletion in the orbitalfrontal cortex (Bissonette & Powell, 2012; V. J. Brown & Bowman, 2002;

Colacicco, Welzl, Lipp, & Würbel, 2002; Dias, Robbins, & Roberts, 1996a, 1996b; Kesner & Churchwell, 2011; McAlonan & Brown, 2003; Ragozzino, 2007; Salazar, White, Lacroix, Feldon, & White, 2004) and dopaminergic dysfunction in the striatum (Clarke, Hill, Robbins, & Roberts, 2011; Izquierdo, Brigman, Radke, Rudebeck, & Holmes, 2017). In humans, patients with schizophrenia made more errors following reversal (Pantelis et al., 1999) and required more trials to acquire the IDS (Pantelis et al., 2009) than control participants or patients with prefrontal lobe lesions.

Following the intra-dimensional shift on the IDS, an extradimensional shift (EDS) occurs. The EDS is also referred to as an attentional set-shift because it involves the transition of the discrimination from one stimulus dimension (e.g., color) to another (e.g., shape) (Owen et al., 1991). For rodent EDS, the task often involves a shift from one perceptual dimension (e.g., spatial location of the lever within the chamber) to another (e.g., visual location of a light) (Colacicco et al., 2002). Impaired acquisition of the EDS, which is often due to perseverative responding, is indicative of specific neurological dysfunction. Lesion studies have shown that inactivation of medial prefrontal cortex (Birrell & Brown, 2000; Bissonette & Powell, 2012; Bissonette & Roesch, 2017; Dias et al., 1996b, 1996a; Dias, Robbins, & Roberts, 1997; Owen et al., 1991) and anterior cingulate cortex (Bissonette, Powell, & Roesch, 2013; Bissonette & Roesch, 2017) are important for attentional set-shifting. Poor acquisition of EDS has also been observed in patients with frontal lobe damage (Pantelis et al., 1999), high-functioning autism (Brady et al., 2013) schizophrenia predominated by negative symptoms (Pantelis et al., 1999, 2009) that becomes further impaired with disorder progression (Leeson et al., 2009; Pantelis et al., 2009) and obesity (Cserjési, Molnár, Luminet, & Lénárd, 2007) especially when accompanied by low-grade inflammation (Lasselin et al., 2016).

Measuring Working Memory

Working memory allows stimuli to briefly, on the order of seconds to minutes, occasion behavior in the absence of the controlling stimulus (Barendse et al., 2013; Goldman-Rakic, 1994, 1995). This type of memory is assessed using procedures that require delayed responding. Common procedures include delayed matching to sample (DMTS), which is a component of the CANTAB (Castner, Goldman-Rakic, & Williams, 2004) or the spatially-based rodent analogue of DMTS termed delayed matching to position (DMTP) (Sahakian & Owen, 1992). Like, behavioral flexibility, working memory impairment is indicative of specific neural, especially frontal lobe, dysfunction (Barendse et al., 2013; Castner et al., 2004; Chudasama & Muir, 1997; Correll & Scoville, 1965; Sloan, Döbrössy, & Dunnett, 2006), neuropsychiatric disorders (Chien et al., 2015; Park & Holzman, 1992; Steele, Minshew, Luna, & Sweeney, 2007), diet (Greenwood & Winocur, 1990, 1996; McNeilly, Williamson, Sutherland, Balfour, & Stewart, 2011; Winocur & Greenwood, 1999), and obesity (Winocur et al., 2005). There is also some evidence for developmental programming of adult spatial working memory by MIA (Meyer et al., 2005; Meyer, Nyffeler, Schwendener, et al., 2008; Samuelsson, Jennische, Hansson, & Holmang, 2005).

Both DMTS and DMTP consist of three phases: sample, delay, and choice. In the sample phase, a stimulus is presented and the animal must attend to it (Baddeley & Hitch, 1974; Cowan, 1995; Kastner & Ungerleider, 2000; Petersen & Posner, 2012; Eriksson, Vogel, Lasner, 2015). Often, the animal is required to respond to the sample stimulus as an indication of perception. Impaired performance on this phase of the task can be indicative of sensory, motor, or attentional deficits (Paule et al., 1998; Srimal & Curtis, 2008). Following its presentation, the sample is removed the delay period will begin. During the delay, which can last several centiseconds to

minutes, the animal cannot perform the target response or, depending on the apparatus used, responding is ineffectual. During the delay, hippocampal function is important for recall of the sample stimulus (Dudchenko et al., 2013). Following the delay, at least two response alternatives become available or active and the animal must respond based on the sample stimulus. Commonly this entails choosing the alternative that matches the sample. Prefrontal cortex function is important for performance in the choice phase (Dudchenko et al., 2013).

Immunomodulatory Intervention and Rescue

Given the importance of immune priming in unmasking developmental programming by MIA, interventions that attenuate abnormal immune response in postnatal offspring should afford at least some protection against disordered behavior. In addition to providing greater improvements in behavioral inflexibility than traditional pharmacological interventions, drugs with anti-inflammatory effects show some preventative value (Pointkewitz, Arad, & Weiner, 2012; Pointkewitz, Assaf, & Weiner, 2009; Amminger, Schäfer, Schlögelhofer, Klier, & McGorry, 2015; Zheng et al., 2017). Although most antipsychotic drugs do not produce anti-inflammatory effects, some do (Cazzullo et al., 2002; Maes et al., 1996; Meyer, Schwarz, et al., 2011; Monji et al., 2013; Müller, Empl, Riedel, Schwarz, & Ackenheil, 1997; Sirota, Meiman, Herschko, & Bessler, 2005; Song, Lin, Kenis, Bosmans, & Maes, 2000; Sugino, Futamura, Mitsumoto, Maeda, & Marunaka, 2009). When these anti-inflammatory antipsychotic drugs are administered to experimental models prior to symptom onset, they successfully prevent brain and behavioral dysfunction (Piontkewitz et al., 2012; Piontkewitz et al., 2009). Relatedly,ω-3 reduce the rate of progression to first-episode psychotic disorders (Amminger et al., 2015; Zheng et al., 2017).

Lacto-N-fucopentaose III (LNFPIII) is a Lewis^x trisaccharide containing immunomodulatory glycan secreted by helminth parasites (Bhargava, Li, Stanya, Jacobi, & Dai, 2012; Tundup, Srivastava, Norberg, Watford, & Harn, 2015). LNFPIII potentially activates anti-inflammatory immune activity in the host (Atochina & Harn, 2005; Harn, McDonald, Atochina, & Da'Dara, 2009; E. J. Pearce, 2005; van Riet, Hartgers, & Yazdanbakhsh, 2007; Velupillai, Secor, Hoerauf, & Harn, 1997). Specifically, TLR expression is attenuated (Hartgers et al., 2008; Maizels, 2016; Thomas et al., 2003) and Th-2, or anti-inflammatory, response is sensitized (Harn et al., 2009; Mpairwe, Tweyongyere, & Elliott, 2014).

Gestational LNFPIII exposure has been shown to program a dampened proinflammatory immune response (Elliott et al., 2007; Labeaud, Malhotra, King, King, & King, 2009; Maizels, 2016; Smits & Akdis, 2014), a sensitized anti-inflammatory immune response during postnatal immune challenge (Pit, Polderman, Schulz-Key, & Soboslay, 2000; Thomas & Harn, 2004), and reduced immunity following childhood vaccination (Labeaud et al., 2009). Offspring of maternal helminth infection also show reduced development of disorders characterized by increased proinflammatory immune activity: respiratory allergy (Smits & Akdis, 2014), infant eczema (Elliott et al., 2007), and disordered autoimmune function (Maizels, 2016). Developmental programming of this nature could prove beneficial for attenuating the adverse effects of proinflammatory MIA that is associated with increased risk of ASD, schizophrenia, and obesity in offspring. To date, no studies have assessed whether these immune alterations are sufficient to balance proinflammatory activation and attenuate offspring behavioral or neurological impairments observed following maternal Poly I:C or a maternal diet rich in saturated fatty acids.

Conclusion

Behavioral flexibility is an important aspect of behavior because its inverse, rigidity, is incompatible with learning. Furthermore, working memory is also an important aspect of behavior that is necessary for learning and performing complex behaviors (Baddeley, 1992). Dysfunction in these behavioral domains are also important aspects of some neurodevelopmental disorders including ASD (Russo et al., 2007) and schizophrenia (Goldman-Rakic, 1994; J. Lee & Park, 2005; Leeson et al., 2009; Pantelis et al., 1999). More severe behavioral inflexibility is associated with poorer clinical outcomes (Meyer, Schwarz, et al., 2011; Troyb et al., 2016). The etiology of these disorders and behavioral inflexibility more generally remains unknown, but converging evidence from epidemiological studies and experiments using animal models indicate an important role for the maternal immune system in these offspring outcomes. Importantly the specific event that induces maternal immune activation is less important for fetal outcomes than intensity, timing, and duration of the immune activation (Gilmore & Jarskog, 1997; Meyer et al., 2006).

Whether maternal immune activation is acute or chronic, it readily produces adverse developmental programming in offspring. Immune priming, is of particular interest because greater baseline inflammation and sensitized immune response to proinflammatory stimuli have been associated with generally poorer cognitive performance (Crichton et al., 2011; Rajia et al., 2010), ASD (Dodds et al., 2011; Krakowiak et al., 2012; Lyall et al., 2013; Van Lieshout et al., 2011), and schizophrenia (Knuesel et al., 2014; Yolken & Torrey, 1995). The delayed effect of MIA immune priming can account for the delayed onset of symptoms for disorders like ASD and schizophrenia.

Immune priming also identifies a mechanism for intervention – attenuating inflammation in offspring. There is compelling evidence that preventative, rather than corrective, interventions

produce better offspring outcomes (Amminger et al., 2015; Piontkewitz et al., 2012, 2009). Given this information, it seems logical to intervene by reducing proinflammatory cytokine levels concurrent with the proinflammatory insult. In experimental models, implementing such immunomodulatory interventions during gestation have proven tricky. Over-attenuation of proinflammatory cytokines produces adverse offspring outcomes in its own right (Meyer, Schwarz, et al., 2011) because these cytokines are necessary for normal development (Bilbo & Schwarz, 2012; Boulanger, 2009; Deverman & Patterson, 2009; Garay & McAllister, 2010; Stolp, 2013).

Interventions that restore homeostatic proinflammatory and anti-inflammatory cytokine balance without reducing levels of proinflammatory cytokines are appealing (Meyer, Schwarz, et al., 2011). In this regard, gestational administration of LNFPIII is appealing because it increases anti-inflammatory cytokine activity, but does not directly reduce levels of proinflammatory cytokines. As such, levels of proinflammatory cytokines would still be elevated, the increased anti-inflammatory cytokine levels would theoretically result in a restoration of homeostatic cytokine balance preventing adverse developmental programming in offspring.

In the current study, offspring will be exposed to either acute or chronic maternal immune activation with the viral mimic poly I:C or a diet high in saturated fatty acids, respectively. Adult offspring will then be assessed on a spatial discrimination reversal task and visual discrimination reversal task to assess two unique aspects of behavioral flexibility: reversal learning and extradimensional set-shifting. Working memory of adult offspring will then be assessed with a delayed matching to position task. Within each exposure group (acute or chronic) some dams will also be exposed to immunomodulatory glycan. Offspring of these dams will also be assessed on the same behavioral measures to determine whether concurrent

activation of antiinflammatory cytokines (glycan) balances or dampens the effect of elevated proinflammatory cytokines (maternal high-fat diet or poly I:C) on behavioral outcomes.

Poly I:C Induced Maternal Inflammation: Sex-Dependent Developmental Programming and Attenuation by Glycan in Adult Offspring

The developing nervous system is especially vulnerable to disruption. Adverse events during this critical period of development can have lasting effects on offspring neural, immune, and behavioral function, which is referred to as developmental programming (Barker, 1997; Calkins & Devaskar, 2011; Gluckman, Hanson, & Spencer, 2005). Proinflammatory maternal immune activation (MIA) is an especially potent disruptor because placental and blood-brain barriers are permeable to these immune factors (Bilbo, 2011; Bolton & Bilbo, 2014; Hsiao & Patterson, 2011; Urakubo, Jarskog, Lieberman, & Gilmore, 2001). Indeed, these immune factors are necessary for normal offspring development (Bilbo, 2011; Bilbo & Schwarz, 2012; Boulanger, 2009; Deverman & Patterson, 2009; Garay & McAllister, 2010; Stolp, 2013).

Deviations from homeostatic levels of immune factors can result in developmental programming of offspring and promote adverse health outcomes including some neurodevelopmental disorders (Ghassabian *et al*. 2018; Hui *et al*. 2018). In humans, MIA as a result of viral infection, especially influenza, has been identified as an important risk factor for the development of autism spectrum disorders (ASD) and schizophrenia in offspring (Meyer, 2014; Patterson, 2011, 2012; Patel et al., 2018). Experimental models involving the direct infection of pregnant rodents with influenza recapitulated epidemiological findings with humans, specifically that infection promoted ASD and schizophrenia-like symptoms in offspring (Meyer & Feldon, 2010; Meyer, Feldon, & Fatemi, 2009). Importantly, the influenza virus was not detectable in fetal tissues, meaning the virus itself was not responsible for adverse offspring developmental programming (Fatemi et al., 2012; Shi, Tu, & Patterson, 2005).

Findings from subsequent studies infecting pregnant dams with the viral mimic

polyinosinic:polysytidylic (Poly I:C) acid, a synthetic analog of double-stranded RNA and a potent TLR-3 receptor agonist (Alexopoulou, Holt, Medzhitov, & Flavell, 2001) indicated that MIA and not influenza itself was responsible for adverse proinflammatory developmental programming in offspring (Buka et al., 2001; Gilmore & Jarskog, 1997; Patterson, 2009; Pearce, 2001). Studies using Poly I:C to induce MIA recapitulate findings with influenza infection, namely impaired behavioral flexibility (Amodeo et al., 2019; Canetta et al., 2016; Choi et al., 2016; Han, Li, Meng, Shao, & Wang, 2011; Malkova, Yu, Hsiao, Moore, & Patterson, 2012; Meyer, Feldon, Schedlowski, & Yee, 2005; Rose et al., 2017; Wallace, Marston, McQuade, & Gartside, 2014; Zhang & van Praag, 2015) and impaired spatial matching to position (Meyer & Feldon, 2009; Richetto, Calabrese, Meyer, & Riva, 2013), spatial non-matching to position (Murray *et al*. 2017), and prepulse inhibition (Bates *et al*., 2018; Ding *et al*. 2019). The Poly I:C model also recapitulates sex differences in behavioral outcomes observed in humans with ASD and schizophrenia. Often, male offspring of dams exposed to Poly I:C (up to 20 mg/kg) mid-gestation (E 9.5 to E 12.5) show increased perseverative behavior (Xuan & Hampson, 2014; Barke *et al*., 2019; Estes *et al*., in press). Although it is unclear whether Poly I:C directly interacts with the fetal immune system, studies that assess sex-differences in immune activation show sexual dymorphism in patterns of placental inflammation following Poly I:C exposure (Barke *et al*., 2019) and a greater proinflammatory immune response and oxidative imbalance in male offspring (Hui *et al*., 2018).

Importantly, impairment was noted in specific neural regions associated with these behavioral deficits: impaired frontal cortex (Amodeo *et al*., 2019; Ding *et al*., 2019; McColl & Piquette-Miller, 2019) and hippocampal (Ding *et al*., 2019; Gao *et al*. 2019; Hui *et al*., 2018) function. In addition, this model also captures sex bias, with greater effects observed in males

than females, observed for ASD and schizophrenia (McColl & Piquette-Miller, 2019; Hui *et al*. 2018; Barke *et al*., 2019; Hui *et al*., 2018; Yerys *et al*., 2009; Pantelis *et al*., 2009).

Both influenza and Poly I:C models of MIA have been critical for determining periods of vulnerability to adverse developmental programming by MIA in offspring (Meyer, Schwarz, & Müller, 2011). Identifying these windows is important because it highlights important periods during which interventions could be implemented.

Given that non-homeostatic elevation of proinflammatory cytokines during gestation has been shown to induce adverse developmental programming in offspring, interventions that reduce levels of these proinflammatory immune factors should afford protection against disordered behavior. There is some evidence that administering antipsychotic drugs with anti-inflammatory effects reduces the progression to first-episode psychosis in schizophrenia (Amminger, Schäfer, Schlögelhofer, Klier, & McGorry, 2015; Piontkewitz, Arad, & Weiner, 2012; Piontkewitz, Assaf, & Weiner, 2009; Zheng et al., 2017).

It remains unclear whether interventions that restore maternal cytokine balance, at the time of insult, can prevent or greatly attenuate adverse developmental programming in offspring. Such interventions are difficult because over-attenuation of proinflammatory cytokines can produce adverse health outcomes because these factors are necessary for normal offspring development (Boulanger, 2009; Deverman & Patterson, 2009; Garay & McAllister, 2010; Grissom et al., 2014; Stolp, 2013) (Mosser *et al*. 2017).

Interventions that restore homeostatic balance by increasing levels of anti-inflammatory cytokines and without reducing levels of proinflammatory cytokines are appealing (Meyer et al., 2011). One promising compound is Lacto-N-fucopentaose III (LNFPIII), a Lewis^{x} trisaccharide

containing immunomodulatory glycan secreted by helminth parasites and found in human breast milk (Bhargava, Li, Stanya, Jacobi, & Dai, 2012; Tundup, Srivastava, Norberg, Watford, & Harn, 2015; Tundup *et al*., 2012). This compound has been shown to produce developmental programming of a sensitized anti-inflammatory response (Pit, Polderman, Schulz-Key, & Soboslay, 2000; Thomas & Harn, 2004) and dampened proinflammatory response (Elliott et al., 2007; Labeaud, Malhotra, King, King, & King, 2009; Maizels, 2016; Smits & Akdis, 2014).

To date, no studies have investigated whether concurrent administration of the proinflammatory viral mimic Poly I:C and immunomodulatory glycan are sufficient to balance proinflammatory MIA and attenuate offspring behavioral impairments in offspring. We predict that gestational exposure to Poly I:C will impair intradimensional shifting on a spatial discrimination reversal task and extradimensional shifting on a visual discrimination, as well as impair working memory at longer, but not shorter delays. Furthermore, concurrent administration of glycan and Poly I:C should result in a dampening or complete reversal of these effects. Namely animals administered Poly I:C and glycan should be statistically indistinguishable from control or their performance should fall between the other two groups. Finally, if sex differences do occur as a function of Poly I:C, we expect that males show greater impairment, as this would recapitulate sex differences observed in the incidence of ASD and schizophrenia observed in humans, as well as obseved sex-differences in behavioral, neural, and immune outcomes following prenatal Poly I:C exposure (Hui *et al*., 2018; Xuan & Hampson, 2014; Barke *et al*., 2019).

Methods

Breeding and Exposure

C57Bl/6 mice were mated at University of Georgia until a sperm plug was detected, which marked embryonic day 0 (E0). Throughout gestation and lactation, dams were exposed twice weekly to either a dextran vehicle or to an immunomodulatory sugar, glycan, which is LNFPIII conjugated to dextran (35 μg/mouse of LNFPIII or vehicle at each dosing). All dextran or glycan injections occurred twice weekly and were administered subcutaneously. Injection volume was 5μl/g maternal body weight. In addition, acute maternal inflammation was induced on E12.5 with 20mg/kg intraperitoneal injections of the potent immune stimulant and viral mimic Poly I:C. This dosing regimen generated three exposure conditions: Dextran + Saline (D+Saline), Dextran + Poly I:C (D+Poly I:C), and Glycan + Poly I:C (G+Poly I:C). Mice were bred until there were sufficient animals for behavioral testing at Auburn University. All breeding and exposure procedures were approved by the University of Georgia Institutional Care and Use Committee and complied with the National Institutes of Health guide for the care and use of laboratory animals.

Subjects

Subjects were 39 (20 female and 19 male) C57Bl/6 offspring of dams in D + Saline, D + Poly I:C, or G + Poly I:C exposures. Offspring were housed at University of Georgia until being shipped to Auburn University, an AAALAC-accredited facility with a 12-hr light-dark cycle, on PND 100-130. Upon arrival animals were group housed by treatment and sex with up to four mice per cage and placed in quarantine for 67 days. Throughout quarantine, animals had free access to food and water, but were separated, by a plexiglass partition, if they became aggressive with cagemates. As quarantine ended, body weights were gradually reduced to 22.0g +/- 2.0g for females and 25.0g +/- 2.0g for males. Following body conditioning and caloric restriction,

animals began behavioral testing at approximately P190. All behavioral procedures were approved by the Auburn University Institutional Care and Use Committee and complied with the National Institutes of Health guide for the care and use of laboratory animals.

Apparatus

Behavioral testing was conducted in 11 Med Associates® (St. Albans, VT) rat operant chambers modified for mice. Each chamber was equipped with two retractable levers, a non-retractable lever, an alcove for liquid-reinforcement delivery, two light emitting diodes (LED), a houselight, and two Sonalert® tone generators (2900 Hz and 4500 Hz). The alcove for liquid-reinforcement was located on the center panel of the front wall and dispensed 0.1cc of 3:1 water:sweetened-condensed milk solution. The houselight was located above the alcove at the top of the chamber. A retractable lever was located on either size of the alcove and there was an LED above each retractable lever. The 2900 Hz tone was located at the top of the chamber above the left retractable lever while the 4500 Hz tone was located at the top of the chamber above the right retractable lever. The non-retractable lever was located on center panel of the back wall of the chamber. Each chamber was located within a sound-attenuating cubicle and a fan was located in the upper-left corner of the right cubicle wall, to ensure air circulation. A Windows® computer, located in the adjacent room controlled all experimental events with 0.01s resolution.

Procedure

Autoshaping.

Beginning on P190, mice began daily 4-hr sessions training on an autoshaping procedure

to establish lever-pressing. Autoshaping sessions began with a 300s inter-trial interval (ITI), during which the houselight and LEDs were darkened, tones were off, front wall levers were retracted, and the back wall lever was inactive, but accessible. Following the ITI, was a 30s pairing interval. At the beginning of the 30s, the houselight and LED above the active lever illuminated, the active lever (e.g., left lever) extended, and the 4500 Hz tone sounded for 0.5s. For the last 10s of the 30s interval, the dipper arm raised and 0.1cc milk solution was available. Milk availability was paired with 0.5s 4500 Hz tone. If the mouse pressed the active lever, then milk became immediately available and was paired with the 0.5s 4500 Hz tone. After the animal responds on the lever, or 30s elapsed, another 300s ITI began. Non-contingent milk delivery ended once the animal performed 10 responses on the active lever within a single 4-hr session.

After this criterion had been satisfied, milk was only delivered on a fixed-ratio (FR) 1 schedule of reinforcement. During FR 1 reinforcement, the houselight and LED above the active lever illuminated and the active lever was extended for the entirety of the session. FR 1 training for the active lever was complete when the animal performed 40 responses within a single 4-hr session, but these 40 responses do not need to occur during the same session as the 10 autoshaping responses. Non-contingent milk delivery in autoshaping only occurred for the first lever trained. For the last two levers trained, milk was only delivered according to an FR 1 schedule of reinforcement. The order that the first two levers were trained was counter-balanced by gestational exposure and sex. The levers on the front wall were always trained first and the lever on the back wall was always trained last. Once the animal performed 40 responses under the FR 1 contingency for all three levers, this aspect of training ended and chain training began.

Chain Training.

Chain Training began once responding had been established on all three levers. The purpose of chain training was to establish a two response behavior chain, a necessary component for IDS and EDS procedures. In the initial link of the chain, the mouse must respond on the back lever. This response caused one of the front levers to extend in the terminal link of the chain. Responding on the extended front lever, in the terminal link, resulted in 3s primary reinforcer (milk) availability. This behavior chain was trained using backward chaining, i.e., starting with the terminal link. On each trial, one of the levers located on the front wall was pseudorandomly presented meaning a lever was not presented on more than two consecutive trials. Once the active lever had extended the mouse had 300s to respond on the extended lever before it retracted. If the mouse responded within 300s, then milk was available for 3s and its availability was be paired with a 0.5s 4500 Hz tone. Failure to respond within 300s resulted in lever retraction and caused the ITI to begin. Each trial was followed by a 10s ITI in which all devices in the chamber were turned off or inactive. Once mice responded 12 times on both front wall levers, the initial link of the behavior chain, i.e. pressing the back lever, was added.

In the initial link an alternating 2900 Hz tone sounded (on 0.3s, off 0.3s). The mouse had 300s to respond on the lever located on the back wall. Responding on the back wall lever caused the alternating tone to terminate and the active front lever to extend. To complete the chain, the animal was required to respond in the terminal link within 300s. Failure to respond within 300s in the initial or terminal link resulted in a 10s ITI and a new trial began. Chain training ended when the mouse performed 50 two-response chains within a single session for three consecutive sessions.

Behavioral Flexibility.

Two procedures were used to assess behavioral flexibility: a spatial discrimination reversal task followed by a visual discrimination task. For both tasks, sessions included 60 trials separated by a 10s ITI and lasted no longer than 30m. As in chain training, each trial consisted of two phases: a trial initiation phase (initiation link) and a choice phase (terminal link). The trial initiation phase was identical to chain training, except that the animal was required to press the back wall lever within 15s. If the trial was initiated, then the choice phase began. In the choice phase, both levers on the front wall were extended and at least one of the LEDs located above the retractable levers illuminated. Both LEDs were illuminated in spatial discrimination reversal learning while only one was illuminated in visual discrimination.

Intradimensional shift: Spatial Discrimination with Reversal.

In order to assess intradimensional shifting (IDS), the mouse first acquired a spatially defined discrimination, termed an original discrimination (OD). In the choice phase of spatial discrimination trials, both front wall levers extended and the LED above each lever illuminated, but only one of the levers was active, for example the lever to the right of the milk alcove. The spatial location of the active lever in OD was counterbalanced by gestational exposure and sex. A correct choice, i.e., responding on the right front wall lever during the choice phase produced 3s access to milk. In contrast an incorrect choice, or error, i.e., responding on the left front wall lever during the choice phase ended the trial. Each trial, independent of outcome was followed by a 10s ITI. Failure to respond in trial initiation or choice phases, both omissions, ended the trial and initiated the ITI.

The OD was to be completed when the mouse responded correctly on 51 of 60 trials for three consecutive sessions. Once these criteria were met, the discrimination would reverse along

the same spatial dimension: if the active lever in the OD was located on the right front wall, the active lever in the first reversal was located on the left front wall. The first reversal proceeded until the mouse again responded correctly on 51 of 60 trials for three consecutive sessions. The discrimination then reversed for a second time, back to the OD contingency and ended once the mouse demonstrated mastery.

A subset of mice failed to satisfy the original accuracy criterion, in which omissions counted, for a reversal because they failed to respond on several trials. For these animals, the contingency was reversed based on accuracy calculations that only included trials on which the animal responded.. Although some animals did omit many trials, when responding did occur it was highly accurate with few errors (Figure 1), which indicates that animals did learn the discrimination. Reversals were only imposed if response accuracy, without omissions included in the calculation, exceeded 85%. All animals met the updated accuracy criterion by the 24th trial (Table 1).

Extradimensional Shift: Visual Discrimination.

Following IDS, mice began a visual discrimination task in order to assess EDS. Sessions proceeded in a similar manner as spatial discrimination sessions, with key differences in the choice phase of trials. In the choice phase, both levers on the front wall extended, but only one LED illuminated. The lever under the illuminated LED became the active lever on that trial. Importantly, the location of the active lever pseudorandomly changed from trial-to-trail, but the active lever did not occur in the same spatial location for more than two consecutive trials. Additionally, a correction procedure was implemented following trials that did not end in reinforcement in order to prevent exclusive responding in one spatial location. Specifically, the

trial repeated until a correct choice was made. These correction trials were not included in calculations of accuracy. EDS ended when the animal responded correctly on 51 of the 60 (non-correction) trials for three consecutive sessions.

Delayed Matching to Position (DMTP).

Following the visual discrimination procedure, a delayed match to position (DMTP) procedure was implemented. Trials within DMTP sessions were broken down into three components: sample, delay, and choice. For the sample portion of a trial, the active lever (either left or right) extended and the mouse was required to respond five times on the active lever in order to complete the sample. Successful responding resulted in the retraction of the active lever to retract and initiation one of eight randomly-selected (without replacement) delays (0.01, 2, 4, 6, 8, 12, 16, and 20s). Once the delay was completed, both retractable levers located on the front wall (Left and Right) extended. Correct responding on the lever that was previously extended during the sample caused both levers to retract and the dipper arm to raise for 3s. In contrast, errors entailed responding on the lever opposite that was previously extended during the sample caused both levers to retract, initiating a 3-sec blackout period. This sequence of events was repeated for twelve trials for each of the delays, for a total of 96 trials per session.

Data Analysis.

For both the spatial discrimination with reversal and visual discrimination tasks, dependent measures included the number of trials on which animals responded correctly (correct), responded incorrectly (errors), and failed to respond (omission). For the EDS task, the number of correction trials was also be analyzed. Data was analyzed using linear mixed effects

(LME) with SYSTAT® 13 (SYSTAT Software Inc. Richmond, CA, USA) and the Type I error rate (α) was set to 0.05. LME was used because it better models incomplete repeated-measures data than traditional repeated-measures ANOVA, which was necessary because number of pups and sex ratio varied between litters. Finally, between subjects factors were sex (female or male) and exposure (Dextran + Saline, Dextran + Poly I:C, or Glycan + Poly I:C), while the within subjects factor was session. For the spatial discrimination reversal and visual discrimination tasks, analyses focused on initial sessions, within each phase of the tasks, to assess behavior in transition. For delayed matching to position task, analyses focused on terminal sessions when behavior was in steady-state.

Results

Intradimensional Shift

On any trial there can be a correct response or one of two types of error, commission or omission. Figure 2 shows the mean correct trials across the first five and last three sessions of each phase OD (top), Reversal 1 (middle), and Reversal 2 (bottom). Data are further separated by exposure group with D+Saline (left), D+Poly I:C (center), and G+Poly I:C (right) with sexes plotted separately. When both sexes were included in the analysis the number of corrects increased to a greater degree for G + Poly IC mice than for the two Dextran groups ($F(4, 125) = 4.335$, $p = 0.003$). The additional Exposure by Sex interaction indicated that this increase in correct trials for the G+Poly I:C animals was driven by the males ($F(1, 125) = 6.139$, 0.015).

The middle row of Figure 2 shows the mean correct trials across sessions during Reversal 1. A significant main effect of Exposure and significant Exposure by Sex interaction indicated the increase in correct trials was greater for the two Poly I:C groups than for D+Saline,

which was driven by G+Poly I:C males ($F(1, 128) = 3.938$, $p = 0.049$; $F(4, 128) = 2.862$, $p = 0.026$).

The bottom row of Figure 2 shows the mean correct trials across sessions for each exposure and sex in Reversal 2. As in Reversal 1, the extent to which correct trials increase across sessions was greater for the Poly I:C mice than D+Saline ($F(1, 117) = 4.995$, $p = 0.027$). However, the G+Poly I:C group made significantly fewer correct trials than the D+Poly I:C group as the sessions progressed after Reversal 2 ($F(4, 117) = 3.242$, $p = 0.015$; $F(1, 117) = 4.077$, $p = 0.046$).

Figure 3 shows error data for the three exposure groups (D+Saline, left; D+Poly I:C, center; G+Poly I:C, right) across the three phases (OD, top; Reversal 1, middle; Reversal 2, bottom), with data plotted by sex. In the original discrimination, D+Poly I:C males made significantly more errors than the other exposure groups ($F(1, 126) = 4.667$, $p = 0.033$). For the middle and bottom panel of Figure 3 (Reversal 1 and Reversal 2) there was only a significant main effect of session, the number of errors significantly decreased across sessions for all groups, but there were no exposure or sex differences.

Figure 4 shows the number of omitted trials for each exposure group and sex with each panel, from top to bottom, representing the OD, Reversal 1, and Reversal 2, respectively. The number of omitted trials for males was similar across all three exposure groups but the D + Saline females omitted the most trials and the G + PolyI:C females the fewest. $F(1, 125) = 5.885$, $p = 0.017$; $F(4, 125) = 2.579$, $p = 0.041$; $F(4, 125) = 5.116$, $p = 0.001$; $F(4, 125) = 3.058$, $p = 0.019$).

For the middle panel of Figure 4 (Reversal 1), a significant main effect of Poly I:C ($F(1, 128) = 7.126$, $p = 0.009$). Both Poly I:C groups omitted fewer trials than D+Saline. In addition,

there was a significant Poly I:C by Session interaction ($F(4, 128) = 3.676$, $p = 0.007$), which demonstrated that the degree to which the average number of omitted trials decreased across sessions was greater for the two Poly I:C groups than D+Saline. Reversing the contingency did not affect the overall number of D+Saline omissions. For D+Poly I:C mice, reversing the contingency reduced the number of omitted trials from OD, but there was no sex difference. Finally, the number of omitted trials decreased for G+Poly I:C from OD to Reversal 1, but the females continued to omit more trials than males.

In Reversal 2 (Figure 4, bottom) there was a significant main effect of Exposure ($F(1, 117) = 4.737$, $p = 0.032$). Together, D+Poly I:C animals omitted fewer trials than D+Saline ($F(1, 117) = 4.255$, 0.041). In Reversal 2, there were no sex-differences in omitted trials for D+Saline. There was a fleeting difference between sexes for D+Poly I:C mice in which females omitted more trials than males, on early sessions. Both D+Poly I:C sexes omitted near zero trials as sessions progressed. Finally, G+Poly I:C mice omitted a similar number of trials as D+Saline. For this group, females tended to omit more trials than males, but this sex difference failed to reach statistical significance.

Extradimensional Shift

Corrects, errors, omissions, and correction trials were compared for the first five sessions of the visual discrimination for the three exposure groups and two sexes. Figure 5 shows the mean correct trials for the three exposures by sex. There was a significant main effect of Session ($F(4, 108) = 33.68$, $p < .001$). For all groups, the number of correct trials increased across sessions. There was also a main effect of Exposure ($F(1, 27) = 10.29$, $p < .01$). The two Poly I:C groups performed significantly more correct trials than D+Saline. There were no effects of anti-inflammatory drug, sex, or significant interactions.

Figure 6 shows the mean error trials across sessions for each Exposure by Sex. There was a main effect of Session; errors decreased across sessions ($F(4, 108) = 7.51$, $p < .001$). There were no other significant main effects or interactions. Figure 7 shows the mean number of omitted trials across sessions for each Exposure group by Sex. There was a significant main effect of session - the number of omitted trials generally decreased as a function of Session ($F(4, 108) = 6.72$, $p < .001$). There was also a main effect of Exposure, with Poly I:C mice omitting fewer trials than D+Saline $F(1, 27) = 9.41$, $p < .01$). There were no other main effects or significant interactions.

Figure 8 shows the mean number of correction trials for each Exposure by Sex across the first five sessions of the visual discrimination. There was a main effect of Session showing that the number of correction trials decreased across sessions ($F(4, 108) = 22.91$, $p < .001$). There was also main effect of Exposure ($F(1, 27) = 8.81$, $p < .01$). Mice exposed to Poly I:C required fewer correction trials than D+Saline, however this difference was driven by the D+Poly I:C group and G+Poly I:C males. G+Poly I:C female responding more resembles D+Saline responding ($F(1, 27) = 5.39$, $p = .03$). There was also a main effect of Sex on number of correction trials and this difference was driven by the poor performance of D+Saline and G+Poly I:C females ($F(1, 27) = 4.29$, $p < .05$).

Delayed Matching to Position

Figure 9 shows response accuracy across exposures and by sex. For all dependent measures there was a significant main effect of delay ($F(7, 240) = 8.848$, $p = 0.005$). For all three Exposures, accuracy decreased as delays increased, which is indicative of delays being sufficiently long to challenge working memory capacity. There were no significant main effects of exposure or sex and no significant interactions.

Discussion

We conducted a thorough and detailed examination of gestational exposure to an acute proinflammatory state as well as concurrent immunomodulation via three behavioral tasks. These tasks were selected because they have been shown to assess executive function and functionality in associated neural regions, in rodents (Brown & Bowman, 2002; Owens et al., 1991; Owens et al., 1992; Bussey et al., 1996; Robbins, 1996; Sahakian & Owen, 1992; Ragozzino, 2007; Pantelis et al., 1999; Russo et al., 2007). The first procedure tested was a spatial discrimination with reversal task, which is a measure of intradimensional shifting and perseverative responding, both of which are important aspects of behavioral flexibility (Dalley, Cardinal, & Robbins, 2004). The second task proceeded from a spatial discrimination reversal task into a visual discrimination task; this procedure has been used as a rodent analogue for extradimensional shifting and cognitive flexibility in humans (Birrell & Brown, 2000; Bissonette & Powell, 2012; Bissonette & Roesch, 2017; Dias et al., 1996b, 1996a; Dias, Robbins & Roberts, 1997; Owen et al., 1991). The third procedure was a delayed matching-to-position task that tested working memory (Sahakian & Owen, 1992; Barendse et al., 2013; Goldman-Rakic, 1994, 1995).

Spatial Discrimination Reversal

For this task, performance under the original discrimination is rarely informative for exposure because deficits are not common. Instead performance on Reversal 1 is of greatest interest. Intact performance involves an increase in errors and decrease in correct responding after the reversal, however animals quickly learn to press the lever in the other spatial location. Delayed learning or the inability to acquire the reversed contingency is indicative of perseverative responding and neurodysfunction (Dalley, Cardinal, & Robbins, 2004; Bissonette & Powell, 2012; Brown & Bowman, 2002; Colacicco et al., 2002; Dias et al., 1996a, 1996b;

Kesner & Churchwell, 2011; McAlonan & Brown, 2003; Ragozzino, 2007; Salazar, white, Lacroix et al., 2004; Clarke, Hill, Robbins, & Robberts, 2011; Izquierdo et al., 2017).

Here, the D+Saline, or control, mice performed worse than either Poly I:C animals on the original discrimination and Reversal 1. Indeed, performance was so poor that we moved forward with Reversal 1 after animals completed 24 sessions regardless of their ability to meet the 85% accuracy criteria. Interestingly, relatively few errors were made throughout the experiment, which indicates that impaired performance was not due to an excess of errors or impaired learning. Instead, impaired performance was driven by an excess of omissions, which could be indicative of poor motivation despite the use of a highly palatable reinforcer (sweetened condensed milk).

The low accuracy due to omissions was a finding driven by the D+Saline mice, which suggests performance was related to motivational differences between groups. Although G+Poly I:C animals did not significantly differ from D+Poly I:C on this task, the G+Poly I:C mice tended to perform better on this task than the D+Poly I:C mice. Under the second and all subsequent reversals group differences due to exposure, where applicable, often resolved or were minimal.

In Reversal 2, groups were mostly indistinguishable despite the finding that the two Poly I:C groups performed somewhat better than D+Saline. On later sessions in Reversal 2, animals in the G+Poly I:C exposure failed to maintain this improved performance. Therefore it is unclear if this difference is spurious or whether glycan attenuated Poly I:C-induced effects by impairing G+Poly I:C performance D+Saline group. Although these effects are not as we predicted, this finding does potentially demonstrate an amelioration of Poly I:C-induced effects by glycan.

Visual Discrimination

Overall, differences in intradimensional shifting observed for the spatial discrimination reversal task were also apparent in extradimensional shifting to a visual discrimination. One striking difference was that the impact of Poly I:C on performance became more apparent with the visual discrimination. The increased sensitivity to Poly I:C exposure is consistent with extradimensional shifts being a more difficult discrimination to acquire than intradimensional shifts, making exposure-related effects more apparent (Owen et al., 1991; Colacicco et al., 2002; Robbins, 2000). Exposure to Poly I:C was associated with improved extradimensional shifting as compared to the D+Saline group and this effect was driven by the number of omitted trials (Figures 7 and 9). This effect of Poly I:C could reflect the changes seen in motivation, which have been observed on breakpoint in other models of the negative symptoms of schizophrenia (Simpson et al., 2011).

An interesting finding was an adverse effect of Poly I:C on errors in males only. Poly I:C males made more errors than D+Saline males. This could mean that the Poly I:C animals had difficulty transitioning from the spatial to the visual discrimination. Alternatively, it could be a result of differences in motivation because these animals responded more and therefore there were more opportunities to respond incorrectly. An increase in errors are to be expected following a change in contingency. This conclusion, regarding changes in motivation, is an appealing one in the context of the generally superior performance for Poly I:C animals. One study assessed the effects of a single midgestation exposure to Poly I:C (4 mg/kg) on motivation in adulthood by comparing the number of omitted trials when reinforcer probabilities were high, low, and during extinction (Bates *et al*., 2018). In this study, control and Poly I:C animals did not differ in the number of omitted trials, however all animals omitted more trials when

reinforcer probability was low and during extinciton. Given the difference in dosing in Bates *et al*., (2018) and the present study, it is possible that changes in motivating operations as a result of Poly I:C exposure only become apparent with greater maternal immune activation.

Delayed Matching to Position

Often, DMTP procedures include a choice-initiation response in which the animal must perform a response (e.g., press a lever) before the two levers extend during the choice phase of the trial. This requirement is important because it forces the mouse to leave the area proximal to the active lever and respond to some other location in the chamber, often equidistant from the two choice levers. Here, this requirement was not included due to excessive omissions observed throughout the experiment during the spatial and visual discrimination tasks. These procedures required the mouse to initiate a trial by responding on a third lever located on the back wall. This response was often omitted by the D+Saline animals during the two behavioral flexibility tasks. Given that response accuracy decreased as a function of delay for all groups, it is unlikely that the mice were sitting in front of the lever presented during the sample for the duration of delay. Furthermore, there were no significant differences in the extent to which delay impaired accuracy for the different exposures or between sexes. There was no effect of gestational exposure to Poly I:C or glycan on working memory as tested here, but it is unclear if including a choice-initiation response would have unmasked differences.

Finally, it is also possible that differences in accuracy are due to attentional differences. Some studies have noted attentional impairment in animals gestationally exposed to Poly I:C (reviewed in Meyer, 2014). This is important because attention deficits can impair performance on a delayed matching task– if the animal does not attend to the sample when it is presented,

then it cannot respond accurately during the choice (White & Wixted, 1999). In the current study, animals were required to respond on the sample lever five times. Although this procedural detail cannot rule-out the possibility of attentional differences, these effects should have been minimal.

Conclusion

There is a wealth of epidemiological evidence demonstrating a relationship between a moderate, acute proinflammatory state during gestation (e.g., influenza) and cognitive deficits, and risk of neurodevelopmental disorders like ASD and schizophrenia (Dodds et al., 2011; Krakowiak et al., 2012; Lyall, Munger, O'Reilly, 2013; Van Leishout et al., 2011; Knuesel et al., 2014; Yolken & Torrey, 1995). These associations have been causally demonstrated and replicated in experimental, mostly rodent, models (Buka et al., 2001; Gilmore & Jarskog, 1997; Patterson, 2009; Pearce, 2001; Meyer, Feldon, et al., 2011). We predicted that gestational exposure to the viral mimic Poly I:C would impair intradimensional and extradimensional shifting, as well as working memory, relative to control D+Saline animals. We also predicted that the concurrent administration of immunomodulatory glycan would rescue or attenuate these Poly I:C-induced deficits. In the present study, differences in performance on the intradimensional and extradimensional shifts were not consistent within or across groups and when differences did occur, they were opposite of the predicted direction.

Animals gestationally exposed to Poly I:C tended to behave more flexibly than the D+Saline animals. One study demonstrated that genetic models of the negative symptoms of schizophrenia had increased breakpoint on a progressive ratio schedule of reinforcement

(Simpson et al., 2011). This is pertinent because when differences were observed between Poly I:C groups and D+Saline, these differences were driven by omissions, not errors.

Another reason for the inconsistency between findings in the literature and the present study, could be due to procedural differences. Often, in the reviewed literature, behavioral flexibility is assessed in mazes or open fields. This is relevant because behaviors assessed in these tasks are biologically prepared (i.e., walking, swimming, or digging). In contrast, the present study assessed an arbitrary response (i.e., pressing a lever).

There are well-established sex-differences in incidence of ASD and schizophrenia, with a higher incidence in males than females. Gestational exposure to Poly I:C in C57Bl/6 mice has been shown to recapitulate these sex differences with males showing neural and behavioral changes that are consistent with these neurodevelopmental disorders (Hui et al., 2018). Here, when improved performance was observed for the Poly I:C exposures, it was driven by males, while impaired performance was driven by females. One recent study by Estes and colleagues (in press), could shed light on these findings. Estes *et al*. (in press) assessed baseline differences in immune response of female C57Bl/6 mice. They found considerable variability in maternal immune biomarkers, which were correlated with maternal IL-6 response and with offspring outcomes following prenatal Poly I:C exposure. There was considerable variability in immune biomarkers between mice obtained from different vendors and that these biomarkers were associated with differential response to Poly I:C exposure and subsequent outcomes in offspring. Whether individual differences in maternal immune response to Poly I:C played a role in offspring outcomes in this study is not clear, but future research in this area should collect data on maternal immune biomarkers and offspring outcomes to determine the replicability and relevance of these findings in maternal immune activation models.

High-Fat Diet Induced Maternal Inflammation: Sex-Dependent Developmental Programming and Attenuation by Glycan in Adult Offspring

Obesity is a major and growing health concern in industrialized nations. There is little evidence for a genetic contribution to the etiology of obesity in humans (Hill & Peters, 1998). Instead life-style factors like diet and inactivity better account for rapidly increasing rates of obesity (Dyer & Rosenfeld, 2011; Ogden, Carroll, Fryar, & Flegal, 2015). This rise in obesity is important because it is a major risk factor for a variety of adverse health outcomes (Armitage, Taylor, & Poston, 2005; Cottrell & Ozanne, 2008; Das, 2001; Schulz, 2010) and cognitive impairments (Hargrave, Jones, & Davidson, 2016).

Adipose is an endocrine organ that secretes immune factors (Das, 2001; Hariri & Thibault, 2010; Parimisetty et al., 2016). Typically, the levels of proinflammatory and anti-inflammatory factors secreted from adipose are balanced, but as excess adipose accumulates this balance tips in favor of a chronic proinflammatory state (Das, 2001; Parimisetty et al., 2016). Elevated levels of proinflammatory factors are relevant to cognitive impairment because it increases blood-brain barrier permeability inducing a state of neuroinflammation (Buckman et al., 2014; Heneka & Nicotera, 2016; Pepping, Freeman, Gupta, Keller, & Bruce-Keller, 2013; Stolp et al., 2011) that can impair cognitive function (Marqués-Iturria et al., 2013; Miller & Spencer, 2014; Pepping et al., 2013).

When obesity occurs in the maternal host, this chronic low-grade inflammation has also been shown to produce adverse health and behavioral effects in offspring (Alfaradhi & Ozanne, 2011; Bilbo & Tsang, 2010; Cottrell & Ozanne, 2008; Davidson et al., 2013; Gillette-Guyonnet et al., 2007; Hargrave et al., 2016; Lee et al., 2010; Nivoit et al., 2009; Vucetic, Kimmel, Totoki, Hollenbeck, & Reyes, 2010) through a process referred to as developmental programming

(Barker, 1997). This developmental programming can result in the permanent alteration of immune, neural, and/or endocrine function (Bilbo & Schwarz, 2009; Bilbo & Tsang, 2010; Lucas, 1994). Indeed, maternal obesity has been shown to increase the risk of disorders that promote chronic inflammation (Alfaradhi & Ozanne, 2011; Bilbo & Tsang, 2010; Cottrell & Ozanne, 2008; Elahi et al., 2009; Hargrave et al., 2016; Nivoit et al., 2009; Samuelsson et al., 2008; Vucetic et al., 2010; Yu et al., 2011) in what has been described as a vicious circle (Davidson, Kanoski, Walls, & Jarrard, 2005; Kanoski, 2012; Sellaro & Colzato, 2017). In addition, maternal obesity has been shown to increase the risk of general cognitive delay (Davidson et al., 2013; Gillette-Guyonnet et al., 2007; Hinkle et al., 2012; Kang, Kurti, Fair, & Fryer, 2014; Lee et al., 2010), and some neurodevelopmental disorders like autism spectrum disorders (ASD) and schizophrenia in offspring (Dodds et al., 2011; Khandaker, Dibben, & Jones, 2012; Krakowiak et al., 2012; Van Lieshout, Taylor, & Boyle, 2011).

Given the limited evidence for a genetic role in the etiology of obesity, diet-induced obesity has become the preferred method for modeling maternal obesity and developmental programming in animal models. Diets that induce maternal immune activation and obesity have been shown to increase the risk of ASD in humans (Lyall, Munger, O'Reilly, Santangelo, & Ascherio, 2013). Although there are a variety of diets that induce obesity, those high in saturated fatty acids, like lard, are especially important because they can induce a proinflammatory state prior to the onset of obesity (Münzberg, Björnholm, Bates, & Myers, 2005; Thaler et al., 2011; Williams, Seki, Vuguin, & Charron, 2014). This is important because it allows for the study of maternal immune activation on developmental programming without concurrent adverse health effects due to obesity and related disorders (Ashino et al., 2012; Volpato et al., 2012).

Gestational exposure to a high-fat diet recapitulates findings observed with developmental

programming due to obesity (Lasselin et al., 2016). Namely offspring show increased adiposity (Akagiri et al., 2008), elevated levels of proinflammatory cytokines (Cani et al., 2007; Cintra et al., 2012; Elahy et al., 2015; Kang et al., 2014; Lumeng & Saltiel, 2011; Manousopoulou et al., 2015; Nerurkar et al., 2011), increased sensitivity to proinflammatory insult (Bilbo & Tsang, 2010; White et al., 2009), and impaired learning and memory (Bilbo & Tsang, 2010; Cordner & Tamashiro, 2015; Kanoski, Meisel, Mullins, & Davidson, 2007; Lu et al., 2011; Mckee, Grissom, Herdt, & Reyes, 2017; Naef et al., 2008; Rodriguez et al., 2012; Tozuka et al., 2010; T. Wu et al., 2013). Together, these findings indicate that inflammation induced by obesity is an important component of adverse developmental programming in offspring. Given the importance of diet or obesity induced inflammation in adverse offspring developmental programming, interventions that attenuate such inflammatory activity are promising. There is promising evidence that postnatal feeding of diets that attenuate the proinflammatory response programmed in gestation can attenuate or reverse adverse outcomes in offspring (Camer et al., 2015; Cintra et al., 2012; Song, 2004; Song, Leonard, & Horrobin, 2004).

To date, there are no studies have assessed whether anti-inflammatory interventions that occur concurrent with the proinflammatory insult can effectively prevent or ameliorate adverse developmental programming. In this regard, parasitic helminth infection is a promising intervention because it potently activates anti-inflammatory pathways in the host (Atochina & Harn, 2005; Harn, McDonald, Atochina, & Da'Dara, 2009; Pearce, 2005; van Riet, Hartgers, & Yazdanbakhsh, 2007; Velupillai, Secor, Hoerauf, & Harn, 1997) by secreting Lacto-N-fucopentaose III (LNFPIII), a Lewis^{x} trisaccharide containing immunomodulatory glycan (Bhargava, Li, Stanya, Jacobi, & Dai, 2012; Tundup, Srivastava, Norberg, Watford, & Harn, 2015). When parasitic helminth infection occurs during gestation, it can result in developmental

programming of an anti-inflammatory response in offspring (Hartgers et al., 2008; Labeaud, Malhotra, King, King, & King, 2009; Mpairwe, Tweyongyere, & Elliott, 2014; Pit, Polderman, Schulz-Key, & Soboslay, 2000; Thomas & Harn, 2004; D. Wu et al., 2011).

Immunomodulatory interventions, like glycan, are also appealing because they do not directly reduce proinflammatory activity – these cytokines are necessary for normal neurodevelopment and their over-attenuation can produce adverse health outcomes in offspring (Bilbo & Schwarz, 2012; Boulanger, 2009; Deverman & Patterson, 2009; Garay & McAllister, 2010; Stolp, 2013). Instead, immunomodulatory glycan increases anti-inflammatory activity (Thomas & Harn, 2004). Therefore, it may be possible to prevent or dampen the cytokine imbalance that results from a proinflammatory state during gestation and resulting developmental programming (Meyer, Schwarz, & Müller, 2011).

Methods

Breeding and Exposure

Breeding and exposures occurred at University of Georgia. Starting eight weeks prior to mating, female C57Bl/6 breeders were exposed either a standard laboratory chow diet (LFD) (10% kcal fat, 70% carbohydrate, 20% protein, D12450J, Research Diets, Inc. New Brunswick, NJ) or a HFD (60% kcal fat, 20% carbohydrate, 20% protein, D12492, Research Diets Inc., New Brunswick, NJ) (Krishna *et al.* , 2016). Sires were fed a LFD diet. Although the two diets differed in percent kcal macronutrient profile, they were isocaloric and micronutrient-balanced. Dietary exposure continued throughout gestation and lactation. After six weeks of dietary exposure throughout gestation and lactation, LFD dams and half of the HFD dams were subcutaneously injected, twice weekly, with dextran vehicle. The other half of HFD dams were

also subcutaneously injected, twice weekly, but with an immunomodulatory sugar, glycan, which is an LNFPIII conjugated to dextran. This produced three exposure groups: Dextran with standard chow (D+LFD), dextran with high-fat diet (D+HFD), and glycan with high-fat diet (G+HFD). Both LNFPIII-dextran and dextran vehicle injection volume were 5 µl/g bodyweight. Breeding and exposure continued until sufficient offspring, at least 10 females and 10 males in each exposure group, were generated for behavioral testing at Auburn University. All breeding and exposure procedures were approved by the University of Georgia Institutional Care and Use Committee and complied with the National Institutes of Health guide for the care and use of laboratory animals.

Subjects

The above described dosing regimen yielded a 2 (Diet) x 2 (immunomodulator) x 2 (sex) design. There were 21 mice in the D+LFD group, 11 female and 10 male; 19 mice in the D+HFD group, 9 female and 10 male; and 21 mice in the G+HFD group, 11 female and 10 male. All mice were shipped to Auburn University between postnatal day (PND) 100 and PND 130. Upon arrival, mice were placed in quarantine in an AAALAC accredited facility with a 12-hr light-dark cycle (lights on at 6:00am). Animals were group housed by treatment and sex for 67 days with up to four mice per cage. Two animals were separated by a plexiglass partition because they became aggressive in group housing. After the 67 day quarantine, animals were introduced to the general Auburn University mouse colony. Animals had ad libitum access to food and water in their home cages until the end of quarantine when body weights were gradually reduced to 22.0g ± 2.0g for females and 25.0g ± 2.0g for males, in order to establish food as an effective reinforcer for behavioral testing. Behavioral testing began at approximately PND 190. All behavioral procedures were approved by the Auburn University Institutional Care

and Use Committee and complied with the National Institutes of Health guide for the care and use of laboratory animals.

Apparatus

Experimental procedures were conducted in 11 Med Associates® (St. Albans, VT) rat operant chambers modified for mice. Each chamber was equipped with two retractable levers on the front wall panel to the right or left of an alcove for liquid-reinforement delivery. A light emitting diode (LED) was located above each retractable lever. A non-retractable lever was located on the back wall center panel, directly across from the liquid-reinforcement alcove. Liquid-reinforcement consisted of one 0.1-cc presentation of a 3:1 water:sweetened-condensed milk solution. At the top of the chamber front wall a houselight was located on the center panel and two Sonalert® tone generators (2900 Hz and 4500Hz) were located on either side of the houselight. The low-tone was located on the left side while the high-tone was located on the right side of the houselight. Each chamber was enclosed in a sound-attenuating cubicle with an air-circulating fan in the upper left corner of the right wall. A Windows® computer, located in an adjacent room, controlled all experimental events with a 0.01s resolution.

Procedure

Autoshaping.

Beginning on PND 198 to 200, mice began training daily in a 4-hr autoshaping procedure to establish lever-pressing on each of the three levers. The order in which animals were trained to press levers was counter-balanced by gestational exposure and sex. Due to its distance from the milk alcove, the back lever was always trained last. Therefore, training order of levers was right, left, then back for half of the mice, while the other half of the animals

experienced left, right, then back.

Autoshaping sessions began with a 300s inter-trial interval (ITI), during which the houselight and LEDs was darkened, tones did not sound, right and left levers were retracted, and the back lever was inactive. After the ITI, the house light turned on, the active lever (e.g., left lever) extended, the LED above the active lever illuminated, and the 4500 Hz tone sounded for 0.5s. For the last 10s of this 30s interval, the dipper arm raiseed making 0.1cc milk solution available. Availability of milk was paired with 0.5s 4500 Hz tone. If the mouse pressed the active lever during the 20s before milk was non-contingently delivered, then milk became immediately available and was be paired with the 0.5s 4500 Hz tone. After the 30s interval or response on the lever, another 300s ITI began.

Animals performed 10 responses on the active lever, within a single 4-hr session, to complete autoshaping. Once this criterion had been satisfied, the animal no longer experienced the autoshaping procedure, i.e., non-contingent milk delivery and pairing of stimuli in the chamber. Instead, milk was delivered according to a fixed-ratio (FR) 1 schedule of reinforcement. The FR 1 training for the left lever was complete when the animal performed 40 responses on the lever within a single 4-hr session. It should be noted that the 40 FR 1 responses did not need to occur in the same session as the 10 autoshaping responses. In addition, autoshaping was only be implemented for the first lever trained. For both subsequent levers (e.g., right and back), training began in the FR 1 component. Once the animal performed 40 responses under the FR 1 contingency on each of the three levers, this aspect of training ended and chain training began.

Chain Training.

Once responding had been established on all three levers, chain training began. The goal of this training was to establish a behavior chain consisting of two responses: responding on the back lever, which caused the right or left lever to extend, and responding on the extended front lever, which resulted in 3s access to milk reinforcement. This behavior chain was trained using backward chaining. Initially, the left or right lever was pseudorandomly presented. The active lever changed from trial to trial, but the same lever was not be presented on more than two consecutive trials in an effort to prevent biasing responding to one side of the chamber. Responding on the extended lever caused the lever to retract, a 4500 Hz tone sounded for 0.5s, and milk was available for 3s. Mice had 300s to respond on the extended lever and failure to respond during this time caused the trial to end and ITI to begin. Each trial was followed by a 10s ITI during which time all devices in the chamber were inactive.

Once mice responded 12 times on the right and left lever, the second link of the behavior chain was added. At this point, a trial began with an alternating 2900 Hz tone (on 0.3s, off 0.3s). Now, the mouse was required to respond on the back lever within 300s. Responding on the back lever terminated the alternating tone and either the left or right lever extended. As before, the mouse had 300s to complete the first link of the chain. If the mouse responded on the right or left lever, milk was available for 3s. If the mouse failed to respond on the right or left lever, the trial ended and the ITI will began. Chain training ended when the mouse successfully performed the 2-link chain 50 times within a session for three consecutive sessions.

Behavioral Flexibility.

Two procedures will be used to assess unique aspects of behavioral flexibility: a spatial discrimination reversal task assessed intradimensional shifting (IDS) and a visual discrimination

task assessed extradimensional shifting (EDS) from the spatial discriminations. For both of these tasks, sessions last approximately 30m and consisted of 60 trials separated by a 10s ITI. Each trial consisted of two phases, first a trial initiation phase, followed by a choice phase. To complete these phases the animal was required to perform the 2-link chain trained in chain training.

In trial initiation, the house light was illuminated and a 2900 Hz tone pulsed (0.3s on, 0.3s off) – indicating that the back lever was active. Failure to respond on the back lever within 15s, referred to as an initiation omission, ended the trial and began the ITI. If the mouse successfully initiated the trial by responding on the back lever within 15s, then the choice phase began. In the choice phase, the 2900 Hz tone stopped pulsing, both of the front wall levers (right and left) extended, and at least one of the LEDs located above the retractable levers illuminated – LED illumination differed between the intradimensional and extradimensional shifting tasks.

Intradimensional Shift.

Spatial Discrimination. The first phase of behavioral flexibility assessment mice first acquired an original discrimination (OD), which was spatially defined. The trial initiation phase proceeded as described above in the behavioral flexibility section. In the choice phase of spatial discrimination trials both levers extended and the LED above each lever illuminated and the mouse was required to press one of the levers within 15s. Failure to respond in the choice phase was referred to as a choice omission. Responding in only one of the spatial locations (e.g., responding on the right lever) produced 3s access to milk, which is referred to as a correct. In contrast, responding to the inactive spatial location (e.g., the left lever), an error, ended the trial and initiated the ITI. The spatial location that was active or inactive during OD was be

counterbalanced by exposure and sex. Each session consisted of 60 trials. The OD was considered acquired when the animal responded with 85% accuracy, or correctly on 51 of the 60 trials, for three consecutive sessions. Once this criterion has been met the contingency will be reversed.

Spatial Discrimination Reversal. Reversal sessions proceeded in a similar manner as OD sessions, with the important exception that the spatial location of the active and inactive lever reversed. If the active lever in OD was located to the right of the milk alcove, then the active lever in the first reversal was be located to the left of the milk alcove. Once performance reached 85% accuracy (51 out of 60 trials were correct) for three consecutive sessions, the contingency again reversed for a second time.

Throughout the experiment, a subset of mice failed to satisfy the original accuracy criterion. In this original calculation, omissions were included and these few mice failed to respond on several trials. Performance for these same mice was, however, highly accurate on the trials on which they did respond, which indicated these mice had learned the discrimination (Figure 10). For these animals, the accuracy criteria was updated such that a reversal was only imposed if accuracy exceeded 85% for three consecutive days, when omissions were excluded from calculations. All animals met this criterion by the 24th session (Table 2).

Extradimensional Shift.

Following IDS, mice began a visual discrimination task in order to assess EDS. This procedure was similar to the one used for IDS, except that the discrimination was visual and not spatial. Responding on the back lever during trial initiation caused both front levers to extend,

but only one LED was illuminated. The lever under the illuminated LED was the active lever, for that trial. In order to prevent exclusive responding on one lever during choice, a correction procedure was implemented. If a trial did not end in reinforcement, then that trial was repeated until a correct choice was made. These correction trials were not included in calculations of accuracy. Aside from correction trials, the location of the active lever was pesudorandomly changed from trial-to-trial, as described in chain training. EDS assessment on the visual discrimination task ended when the animal performed with 85% accuracy for three consecutive sessions.

Delayed Matching to Position (DMTP).

After behavioral flexibility assessment, working memory was assessed with DMTP. For this task, trials consisted of three components: sample, delay, and choice. The sample portion of the trial began with the extension of the active lever (left or right) and terminated with active lever retraction when the mouse performed five responses on the active lever. Upon lever retraction, one of eight randomly-selected (without replacement) delays (0.01, 2, 4, 6, 8, 12, 16, and 20s) was implemented. Once the delay elapsed, the choice portion of the trial began. During the choice, both the left and right levers extended and the mouse was required to respond on one of the levers. Correct responding on the lever that matched the spatial location of the sample caused both levers to retract and the dipper arm to raise for 3s. In contrast, errors entailed responding on the lever opposite the sample caused both levers to retract and initiated a 3-sec blackout period. This sequence of events was repeated for twelve trials for each of the delays, for a total of 96 trials per session.

Data Analysis.

Important dependent measures for both the IDS and EDS task included the number of trials on which animals responded correctly (correct), responded incorrectly (errors), and failed to respond (omission). In addition, the number of correction trials in the EDS task was also be analyzed. For each dependent measure, the between subjects factors was sex (female or male) and exposure (D+LFD, D+HFD, or G+HFD), while the within subjects factor was session. Given the likelihood of unequal sample sizes, data was analyzed using linear mixed effects (LME) because it better models incomplete repeated-measures data than traditional repeated-measures ANOVA. We analyzed data using the full model, which included exposure, sex, and their interaction. Statistical analyses were be conducted using SYSTAT ® 13 (SYSTAT Software Inc. Richmond, CA, USA) and the Type I error rate (α) will be set to 0.05. For the spatial discrimination reversal and visual discrimination tasks, analyses focused on initial sessions, within each phase of the tasks, to assess behavior in transition. For delayed matching to position task, analyses focused on terminal sessions when behavior was in steady-state.

Results

Intradimensional Shift

Figure 11 shows the mean correct trials for each dietary exposure group (D+LFD, left; D+HFD, center; G+HFD, right) for the three phases of the intradimensional shift (OD, top; Reversal 1, middle; Reversal 2, bottom) with data plotted by sex. For the OD (top), there was a significant main effect of session, meaning the number of corrects increased across sessions – an indication of learning ($F(4, 210) = 13.372$, $p < 0.001$). A significant Diet x Sex interaction indicated that despite the overall number of corrects being similar across groups, the number of corrects for dietary exposure depended upon sex ($F(1, 210) = 5.992$, $p = 0.015$). D+LFD,

females made fewer corrects than males of the same exposure while D+HFD females made more corrects than males of the same exposure. This difference decreased as sessions progressed. There was no difference between G+HFD females and males for corrects on the first five trials of OD.

During the first five sessions of Reversal 1 (Figure 11, middle), the number of corrects is low, but increases across sessions for all groups – again indicating learning of the new contingency ($F(4, 212) = 77.130$, $p < 0.001$). There was also a significant Diet x Session interaction ($F(4, 212) = 3.508$, $p = 0.008$). This effect was greater for both HFD groups tha D+LFD ($F(4, 212) = 3.508$, $p = 0.008$), but this finding was not differentially affected by sex. In Reversal 2 (Figure 11, bottom), the number of correct trials, again, increased across the first five sessions for all groups ($F(4, 207) = 167.207$, $p < 0.001$). This increase was greater for males than females as indicated by a significant main effect of Sex ($F(1, 207) = 5.128$, $p = 0.025$). There were no effects of diet on correct trials in Reversal 2.

Figure 12 shows the number of incorrect trials (errors) for each dietary exposure group and sex by OD, Reversal 1, and Reversal 2 (top, middle, and bottom panel, respectively). For the OD, a significant main effect of Session indicated that the number of errors significantly decreased across the first five sessions – an indication of learning ($F(4, 210) = 22.305$, $p < 0.001$). A significant Diet x Session interaction indicated that the degree to which errors decreased across sessions varied as a function of dietary exposure, which was driven by the two HFD groups that made more errors than D+LFD ($F(4, 210) = 2.755$, $p = 0.029$).

In Reversal 1 (Figure 12, middle), the number of errors significantly decreased across the first five sessions for all exposure groups ($F(4, 212) = 79.422$, $p < 0.001$). Although errors decreased for all groups, they decreased to a lesser extent for G+HFD animals than D+HFD or

D+LFD ($F(1, 212) = 4.959$, $p = 0.027$). This effect of glycan on errors did not persist to Reversal 2 (Figure 12, bottom) as there was no effects of diet or sex. Despite this similarity across exposures and sex, all groups showed decreasing errors across the first five sessions of Reversal 2 ($F(4, 207) = 121.923$, $p < 0.001$).

Due to the relatively low number of incorrect trials for all three dietary exposures it would seem the group differences in correct trials are due to differences in omitted trials. Figure 13 shows the number of omitted trials across sessions for each of the dietary exposures and sex for the OD, Reversal 1, and Reversal 2 (top panel, middle panel, and bottom panel, respectively). For the OD there was a slight, overall initial downward trend in omissions for D+LFD mice and a slight initial upward trend in omissions for D+HFD and G+HFD mice, although all OD functions are relatively flat ($F(4, 210) = 3.747$, $p = 0.006$). A significant Diet x Sex interaction indicates that D+LFD females omitted more trials than D+LFD males, but the relationship reversed for both HFD groups on the first three sessions of OD ($F(1, 210) = 4.240$, $p = 0.041$). This relationship did not persist in sessions four and five. A significant Diet x Session interaction indicated that both HFD groups omitted fewer trials than D+LFD ($F(4, 210) = 4.200$, $p = 0.003$).

During Reversal 1, the direction of overall omissions reversed from OD. Omissions for D+LFD remained stable across sessions while there was a slight decrease in the number of omissions for both D+HFD and G+HFD ($F(4, 212) = 5.785$, $p < 0.001$). Furthermore, the sex differences observed during the OD were not present in Reversal 1 (Figure 13, middle). A significant Diet x Session interaction indicated that the two HFD groups omitted fewer trials than D+LFD ($F(4, 212) = 2.627$, $p = 0.036$). The bottom panel of Figure 13 shows the number of omitted trials in Reversal 2. There was a significant main effect of session, which indicated that

omissions decreased across sessions for all groups ($F(4, 207) = 18.692$, $p < 0.001$). There was also a significant main effect of Sex, in which females omitted more trials than males ($F(1, 207) = 4.908$, $p = 0.028$). However this effect was driven by the D+LFD females.

Extradimensional Shift

Figure 14 shows mean correct trials for the first five sessions of visual discrimination for males and females across each exposure group. There was a main effect of session in that corrects increased across sessions ($F(4, 208) = 40.23$, $p < 0.001$). There was also a main effect of sex in which male mice, across exposures, made more correct trials than females ($F(1, 52) = 25.84$, $p < 0.001$). A significant sex by exposure interaction indicated that gestational exposure to a high-fat diet increased correct trials for female mice ($F(1, 52) = 8.41$, $p < 0.01$). There were no other main effects or interactions. Figure 15 shows mean error trials across the exposure groups and sexes for the first five visual discrimination sessions. There was a main effect of session in that errors decreased across sessions which indicated learning ($F(4, 208) = 40.63$, $p < 0.001$). There were no other significant main effects or interactions.

Figure 16 shows mean omitted trials for the three exposure groups by sexes. There were a main effects of session ($F(4, 208) = 3.52$, $p < .01$), exposure ($F(1, 52) = 9.26$, $p < 0.01$), and sex ($F(1, 52) = 16.66$, $p < 0.001$). For all groups, omissions decreased across the first five trials of the visual discrimination. This decrease in omissions was greater for the HFD groups than the D+LFD group and overall females emitted more trials than males. A significant sex by exposure interaction indicated that gestational exposure to high-fat diet decrease omitted trials for females ($F(1, 52) = 8.25$, $p < .01$).

Figure 17 shows mean correction trials for males and females in the three exposure groups. Similar to omitted trials, there were main effects of session ($F(4, 208) = 40.38$, $p <$

.001), exposure ($F(1, 52) = 4.25$, $p < .05$), and sex ($F(1, 52) = 21.38$, $p < .001$). Correction trials decreased across session and this decrease was greater for the high-fat diet groups than D+LFD. Furthermore, females tended to require more correction trials relative to males. A significant sex by exposure which demonstrated that high-fat diet decreased correction trials for females to a greater extent than males ($F(1, 52) = 9.74$, $p < .001$).

Delayed Matching to Position

Figure 18 shows accuracy for the three dietary exposure groups by sex. As the delay increased accuracy decreased, which indicates forgetting at longer delays. There was a significant exposure by delay interaction for females ($F(14, 168) = 1.933$, $p = 0.026$) in which G+HFD females responded more accurately than the two Dextran groups at longer delays.

Discussion

We conducted a detailed examination of gestational exposure to a proinflammatory state as well as prevention or amelioration of these effects by immunomodulation on three behavioral tasks. These tasks were selected because they are putative models of executive function and sensitive to corresponding neural dysfunction, in rodents (Brown & Bowman, 2002; Owens et al., 1991; Owens et al., 1992; Bussey et al., 1996; Robbins, 1996; Sahakian & Owen, 1992; Ragozzino, 2007; Pantelis et al., 1999; Russo et al., 2007). The first procedure tested spatial discrimination with reversal. This task assesses intradimensional shifting and perseverative responding, both of which are important aspects of behavioral flexibility (Dalley, Cardinal, & Robbins, 2004). The second task proceeded from a spatial discrimination reversal into a visual discrimination; one which has been used as a rodent analogue for extradimensional shifting and cognitive flexibility in humans (Birrell & Brown, 2000; Bissonette & Powell, 2012; Bissonette &

Roesch, 2017; Dias et al., 1996b, 1996a; Dias, Robbins & Roberts, 1997; Owen et al., 1991). The third procedure was a delayed matching-to-position task that measures working memory (Sahakian & Owen, 1992).

Spatial Discrimination Reversal

For this task, performance under the original discrimination is rarely informative for exposure because deficits are not common. Instead differences in the extent to which animals acquire Reversal 1 is of greatest interest. Following a reversal, intact performance entails an increase in errors and decrease in correct responding. However, unimpaired animals quickly learn to press the lever in the other spatial location resulting in an increase in correct responding and decrease in errors. Delayed learning or the inability to acquire the reversed contingency is indicative of perseverative responding, neurodysfunction, and an important component of some neurodevelopmental disorders (Dalley, Cardinal, & Robbins, 2004; Bissonette & Powell, 2012; Brown & Bowman, 2002; Colacicco et al., 2002; Dias et al., 1996a, 1996b; Kesner & Churchwell, 2011; McAlonan & Brown, 2003; Ragozzino, 2007; Salazar, white, Lacroix et al., 2004; Clarke, Hill, Robbins, & Robberts, 2011; Izquierdo et al., 2017).

In the present experiment, occasional statistical differences were detected for measures on the spatial discrimination and its reversal, but these differences were not consistent or systematic; overall groups were similar (Figures 11, 12, and 13). All groups demonstrated learning, to an extent. The number of correct trials performed was low following a reversal and increased as sessions progressed. The inverse was demonstrated for incorrect trials. Throughout the experiment, omissions remained high for all groups, with females overall omitting more trials than males and this effect was driven by the D+LFD females.

Visual Discrimination

Overall, differences in intradimensional shifting observed for the spatial discrimination reversal task were also apparent in extradimensional shifting to a visual discrimination. Namely, there were no consistent or systematic differences between the exposure groups in their ability to extradimensionally shift to a visual discrimination (Figures 14, 15, 16 and 17). To an extent there was evidence for acquisition of the visual discrimination in all groups because the number of correct trials generally increased across sessions. However the D+LFD group tended to underperform on this task (Figure 15). Within the D+LFD and G+HFD groups, males performed more correct trials than females, whereas the sexes did not differ within the D+HFD group. For all groups and sexes, errors were low throughout the visual discrimination, which indicates that the superior performance for D+LFD and G+HFD males was due to a reduction in trial omissions. Overall, the D+LFD group underperformed on the extradimensional shift and this effect was driven by the poor performance of females.

To an extent, glycan pulled performance of the G+HFD group in the direction of the D+LFD group. G+HFD females performed more poorly on the visual discrimination than G+HFD males. Given that these differences were a result of excess omissions and not an excess of errors, it is possible that gestational exposure to a high-fat diet improved food-based reinforcement. There is evidence that gestational exposure to a high-fat diet increases the palatability of obesogenic foods, like the high-sugar sweetened condensed milk used as a reinforcer in this study (Grissom et al., 2014; Zhang et al., 2008; DelParigi, Chen, Salbe, Reiman, & Tataranni, 2005; Ong & Muhlhausler, 2011; Sullivan, Smith, & Grove, 2011; Vucetic and Reyes, 2010).

Delayed Matching to Position

For all exposures, response accuracy decreased as a function of delay with few differences in the degree of forgetting. G+HFD females responded more accurately than males of the same exposure, but only at short and intermediate delays. Given that this difference did not persist at longer delays, it is unlikely that it reflects differences in working memory and instead may be the result of some other difference, or is spurious. Often, DMTP procedures include a choice-initiation response. This requirement is important because it forces the mouse to leave the area proximal to the active lever and respond to some other location in the chamber, often equidistant from the two choice levers. Here, this requirement was not included due to excessive omissions observed throughout the spatial and visual discrimination tasks. Both of these procedures required the mouse to initiate a trial by responding on a third lever located on the back wall however, this response was often omitted by the D+LFD females during the two behavioral flexibility tasks. It is possible that this omission of a choice-initiation response dampened the sensitivity of this measure to differences between exposures. That said, it does not appear to prevented the strain on working memory capacity, because accuracy decreased as delays increased.

It is also possible that differences in accuracy are the result of attentional differences. In humans, gestational exposure to obesity is associated with an increased risk of developing attention-deficit hyperactivity disorder (ADHD) (Rivera *et al*., 2015; Hargrave *et al*., 2016). In rodents, maternal HFD resulted in hyperactivity, a symptom of ADHD, in male offspring (Kang *et al*., 2014), however no studies have assessed the relationship between high-fat diet in gestation and attention in offspring. This is relevant because impaired attention can adversely impact performance on a delayed matching task – if the animal does not attend to the sample when it is

presented, then it cannot respond accurately during the choice (White & Wixted, 1999). Here animals were required to perform five responses on the sample lever. This procedural detail cannot rule-out the possibility of attentional differences between exposures, but these effects should have been minimal.

Conclusion

There is a wealth of epidemiological evidence demonstrating an association between a low-grade, chronic proinflammatory state during gestation (e.g., maternal high-fat diet) and an increase in cognitive deficits, as well as risk of neurodevelopmental disorders like ASD and schizophrenia (Cottrell & Ozanne, 2008; Armitage et al., 2005; Schulz, 2010; Hargrave, Jones, & Davidson, 2016; Bilbo & Tsang, 2010; Lasselin et al., 2016;). These associations have been causally demonstrated and replicated in experimental models (Tozuka et al., 2010; Wu et al., 2013; Cordner & Tamashiro, 2015; Bilbo & Tsang, 2010; Lu et al., 2011; Molteni, Barnard, Ying,… 2002; Page et al., 2014; Pini et al., 2016; Robb et al., 2017; Sullivan et al., 2014; Tozuka et al., 2010). We predicted that gestational exposure to a high-fat diet would impair intradimensional and extradimensional shifting, as well as working memory, relative to control D+LFD animals. We also predicted that the concurrent administration of immunomodulatory glycan would prevent or attenuate these dietary-induced deficits.

Under the conditions tested in the present study, there was no evidence of behavioral inflexibility or impaired working memory as a result of gestational dietary or immunomodulatory intervention. One reason for the inconsistency between findings in the literature and the present study, could be due to procedural differences. Often, feeding higher fat diets, like the one used here, will eventually result in obesity (Hariri & Thibault, 2010). Here, mice fed a high-fat diet

gained more weight prior to and throughout pregnancy than LFD mice, however this weight gain was not sufficient for a classification of obesity (data not shown). This deviation from the literature was intentional because we sought to assess the effects of gestational exposure to a high-fat diet in the absence of maternal obesity. This is an important distinction. Obesity has been shown to cause a wide range of health outcomes, endocrine, immune, and neural changes that can impair cognition independent of the macronutrient profile of the diet (Winocur & Greenwood, 1999). Although the dams fed the high-fat diet in this study were found to be insulin resistant, these endocrine changes were insufficient for metabolic syndrome (data not shown).

The findings from this study, or lack thereof, provide further support to the literature demonstrating a no adverse effect threshold for chronic, low-grade inflammation resulting from a diet high in saturated fatty acids in the absence of maternal obesity and obesity-related disorders on higher-order cognitive functions in offspring. White, Purpera, et al. (2009) similarly did not demonstrate developmental programming in offspring gestationally exposed to a high-fat diet in the absence of maternal obesity. Finally, metabolic syndrome is associated with impaired cognitive ability in humans and can cause neurological impairment in experimental models (reviewed in Panza et al., 2010; Farooqui et al., 2012). Insulin resistance is but one aspect of metabolic syndrome and although cognitive deficits can be observed with insulin resistance, these effects are greater when they occur in combination with type 2 diabetes, cardiovascular disease, and hypertension (Winocur & Green, 2005). Importantly the literature investigating the role insulin resistance and metabolic syndrome study are primarily conducted with adult rodents not exposed to these disease states in utero. Therefore, prenatal high-fat diet and insulin resistance in the dam may be insufficient to induce developmental programming on the

endpoints assessed in the present study. Future research should compare maternal obesity and metabolic syndrome due to a high-fat diet, with high-fat diet alone, as well as comparing postnatal metabolic or inflammatory insult in order to better elucidate which aspects of maternal obesity can cause cognitive impairment on the endpoints assessed in this study.

Appendix A
Figures

Figure 1

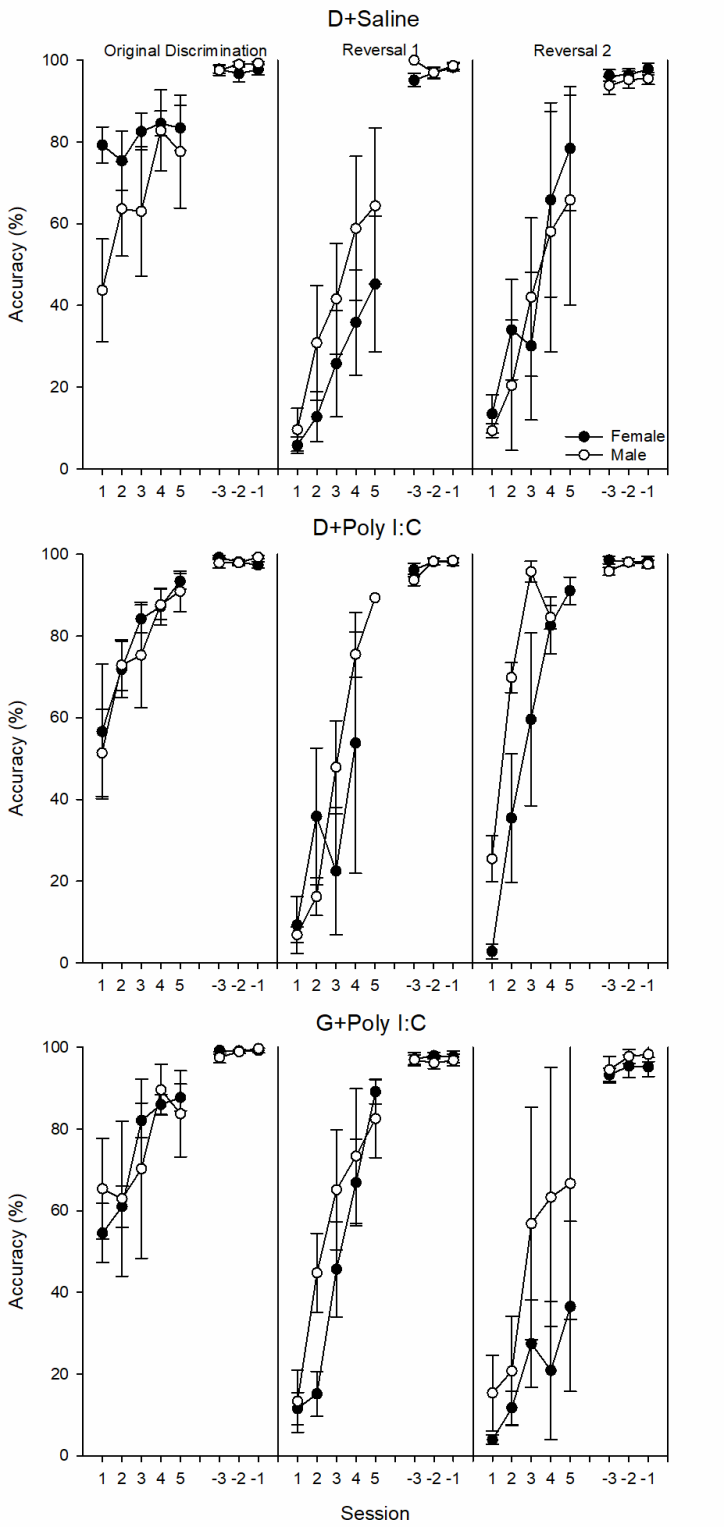
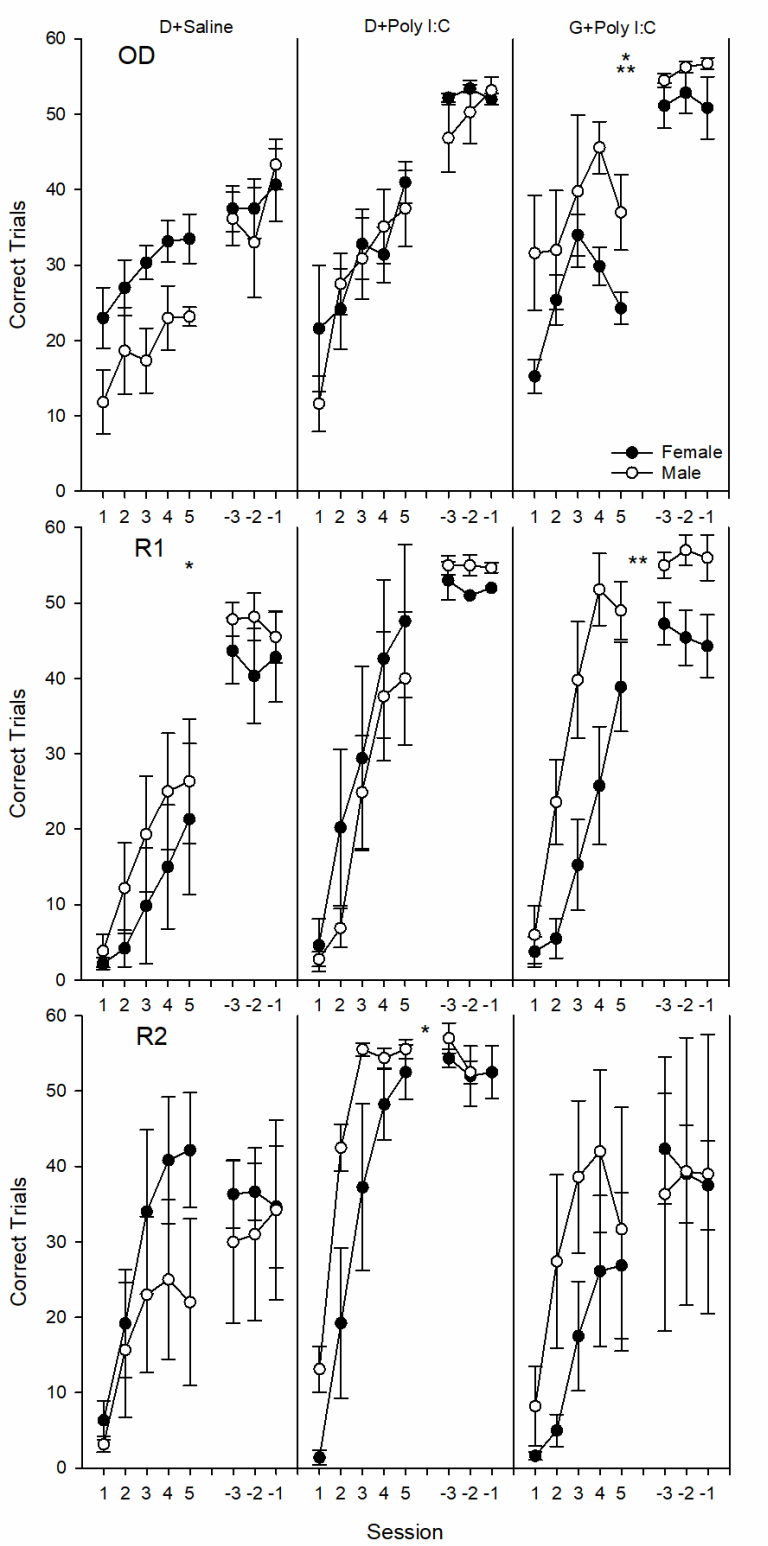


Figure 2


D+Saline
D+Poly I:C
G+Poly I:C
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R1
R2
Correct Trials
Session
Female
Male
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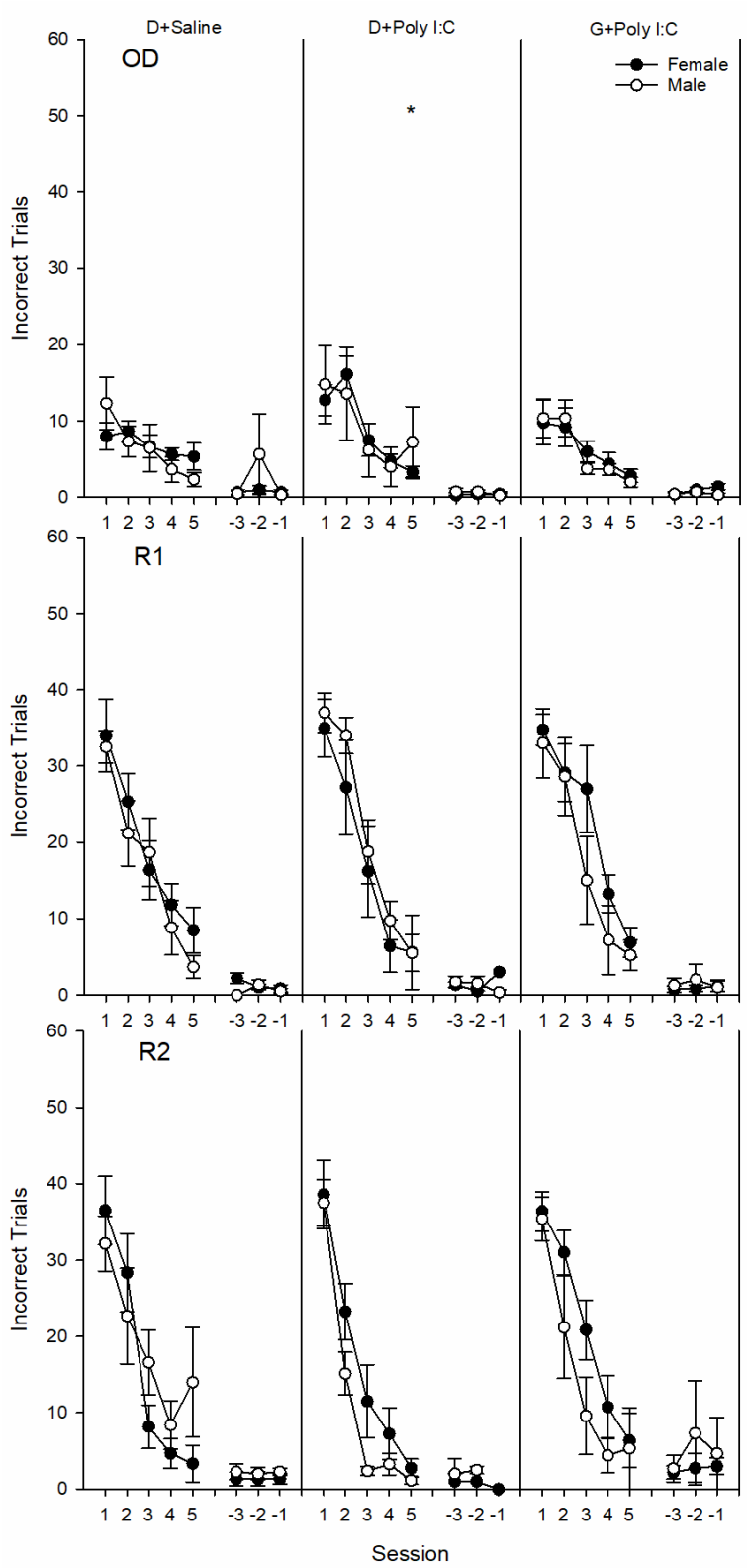
0 10 20 30 40 50 60
* **

Figure 3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G+Poly I:C
OD
R1
R2
Female
Male
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Incorrect Trials
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30
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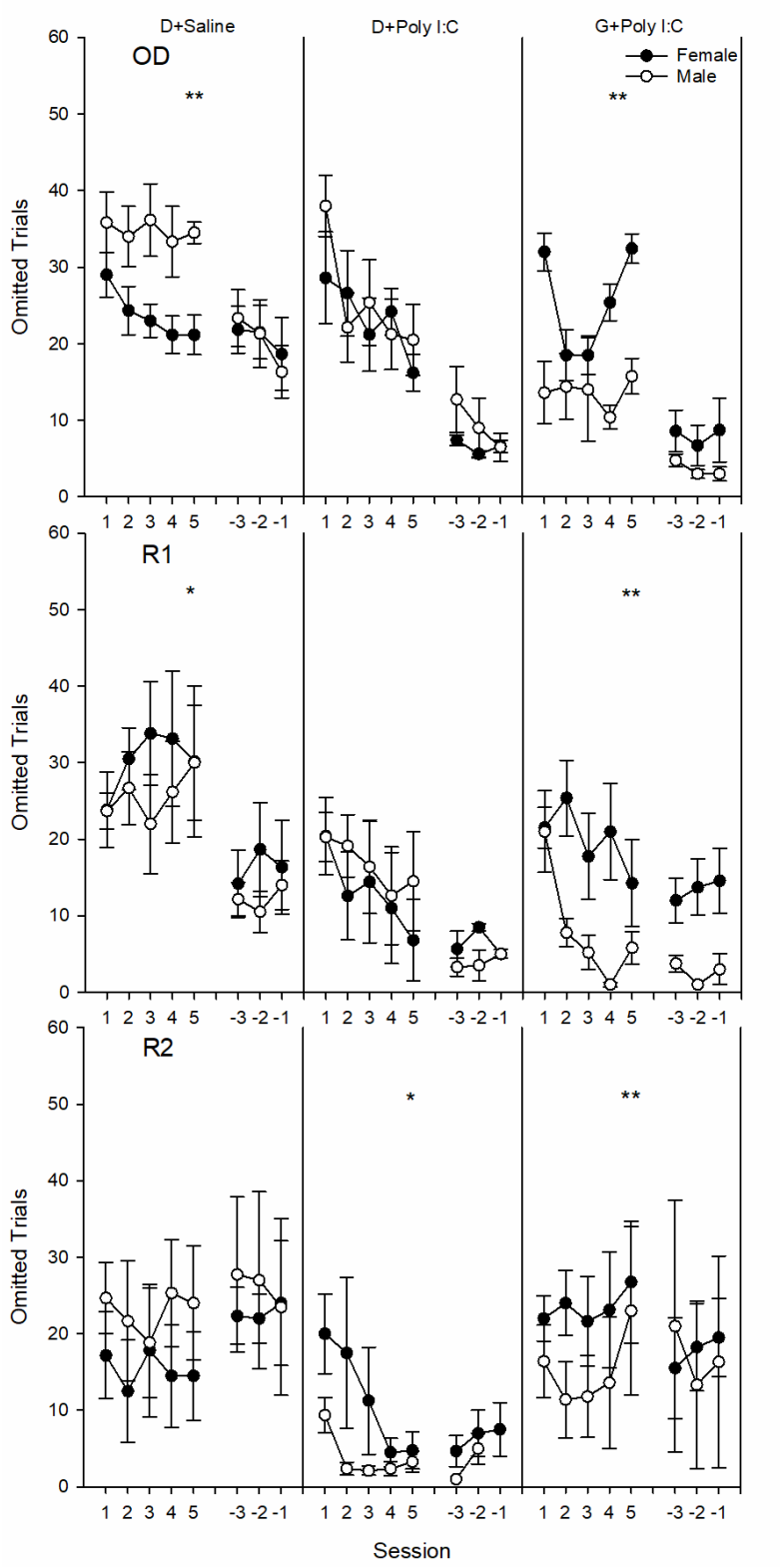
1 2 3 4 5
-3 -2 -1

Figure 4


D+Saline
D+Poly I:C
G+Poly I:C
Female
Male
OD
R1
R2
**
*
Omitted Trials
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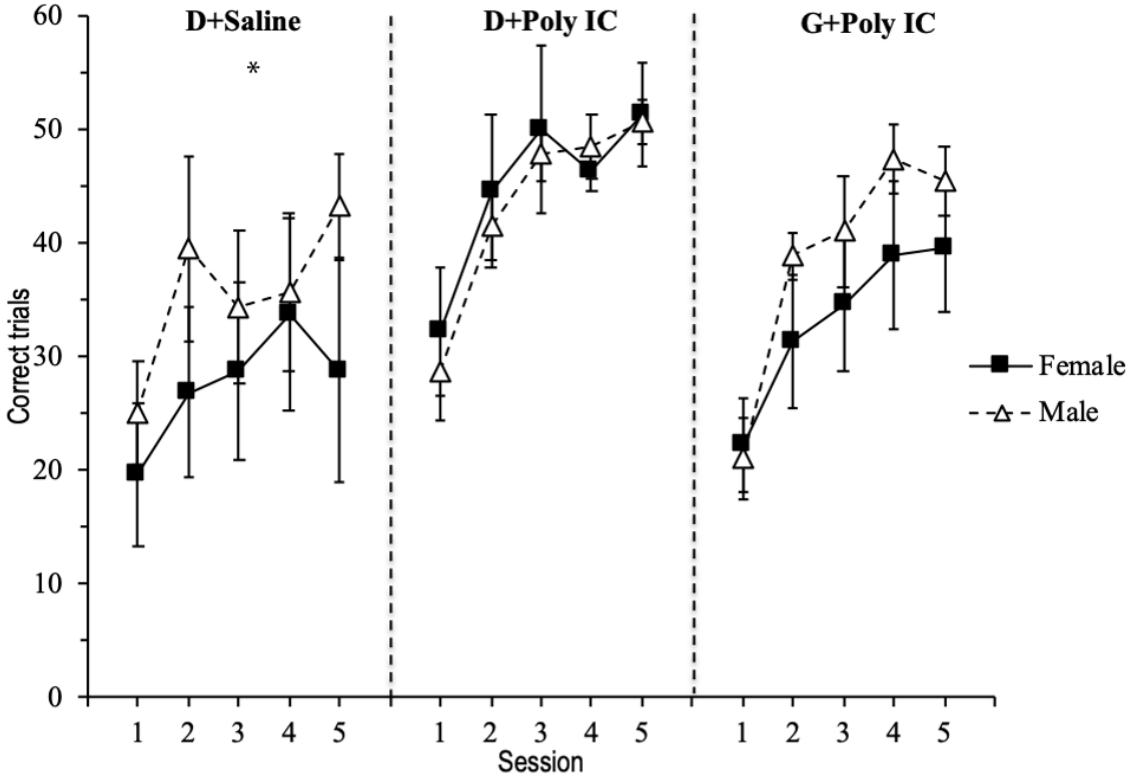
20
30
40
50
60
1 2 3 4 5
-3 -2 -1

Figure 5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D+Poly IC
G+Poly IC
*
Correct trials
Session
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Male
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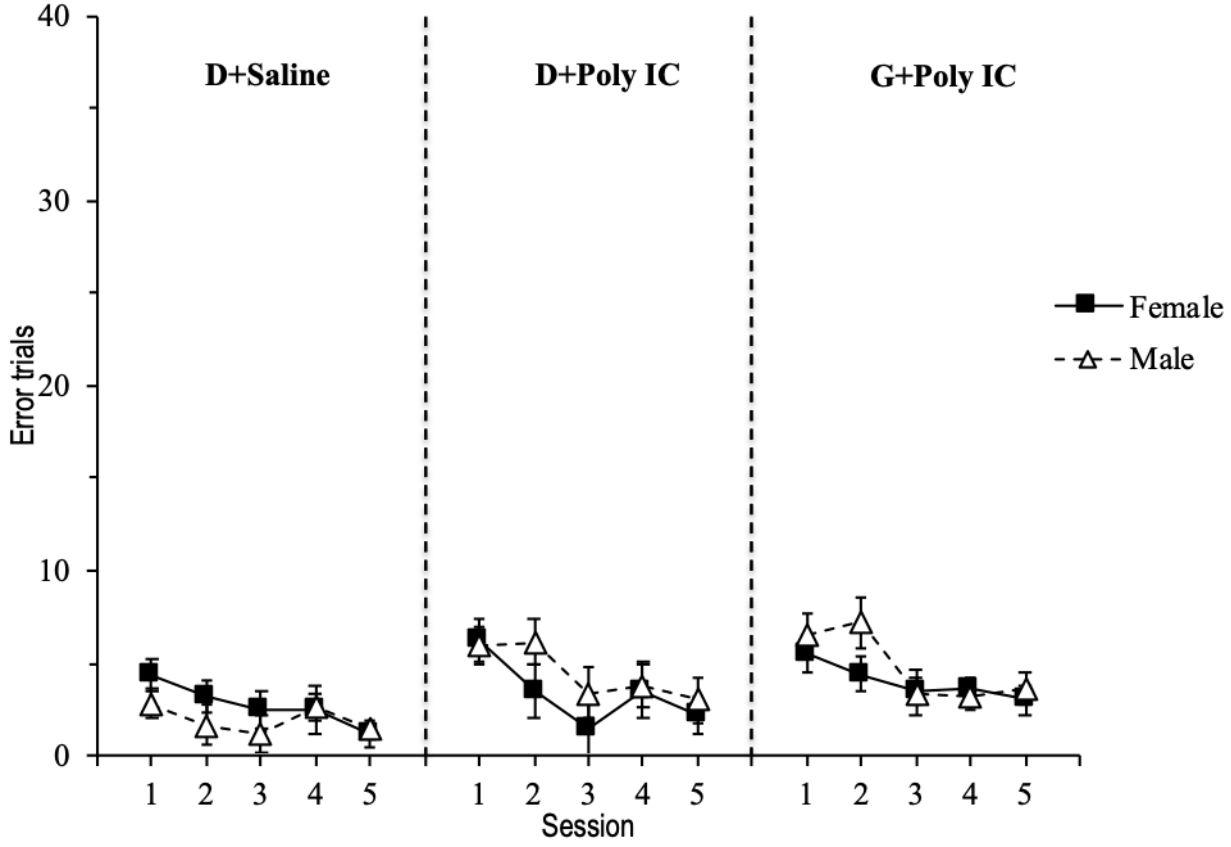
Figure 6.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D+Poly IC
G+Poly IC
Error trials
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30
20
10
0
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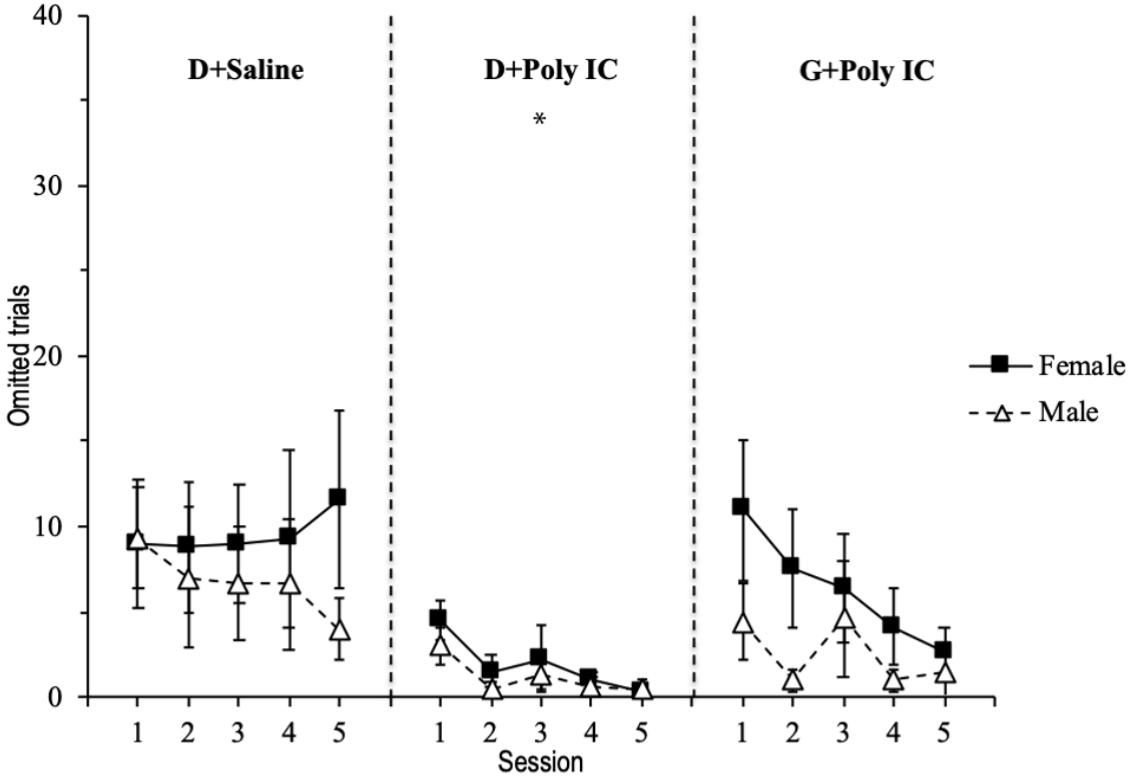
1 2 3 4 5
1 2 3 4 5
Session
Female
Male

Figure 7.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D+Poly IC
G+Poly IC
*
Omitted trials
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30
20
10
0
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1 2 3 4 5
1 2 3 4 5
Session
Female
Male

Figure 8.

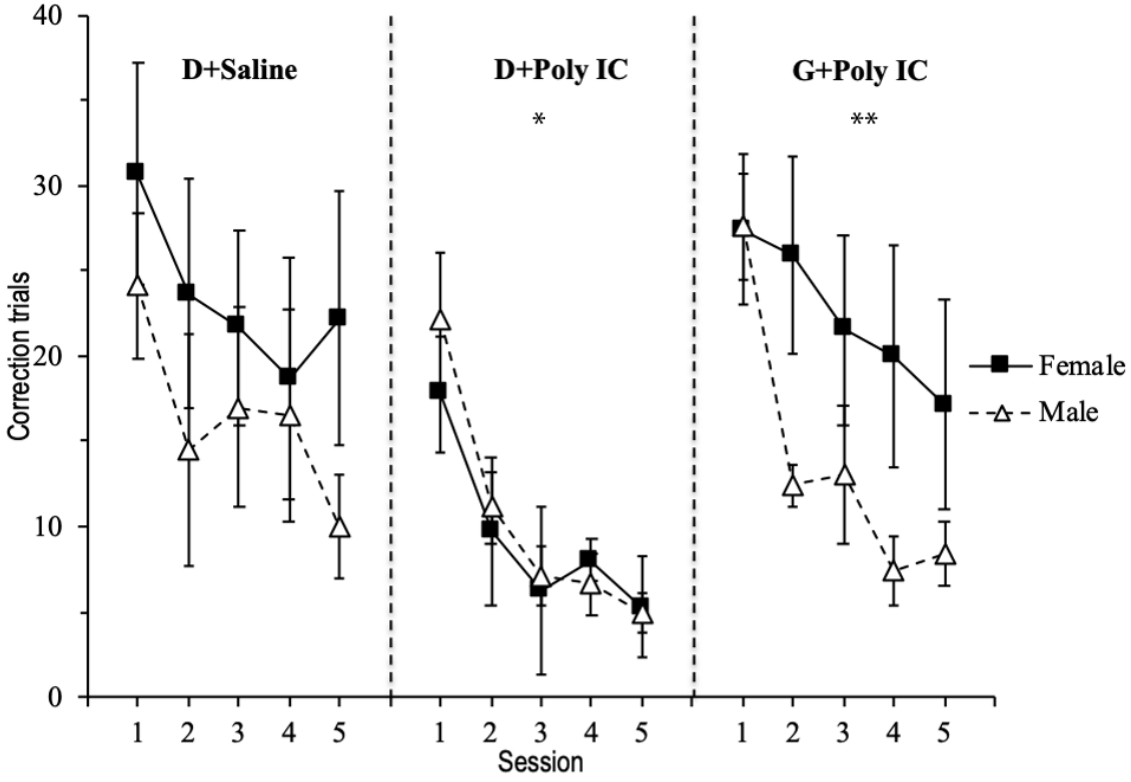

D+Saline
D+Poly IC
G+Poly IC
*
**
Correction trials
Session
Female
Male
0
10
20
30
40
1
2
3
4
5

Figure 9.

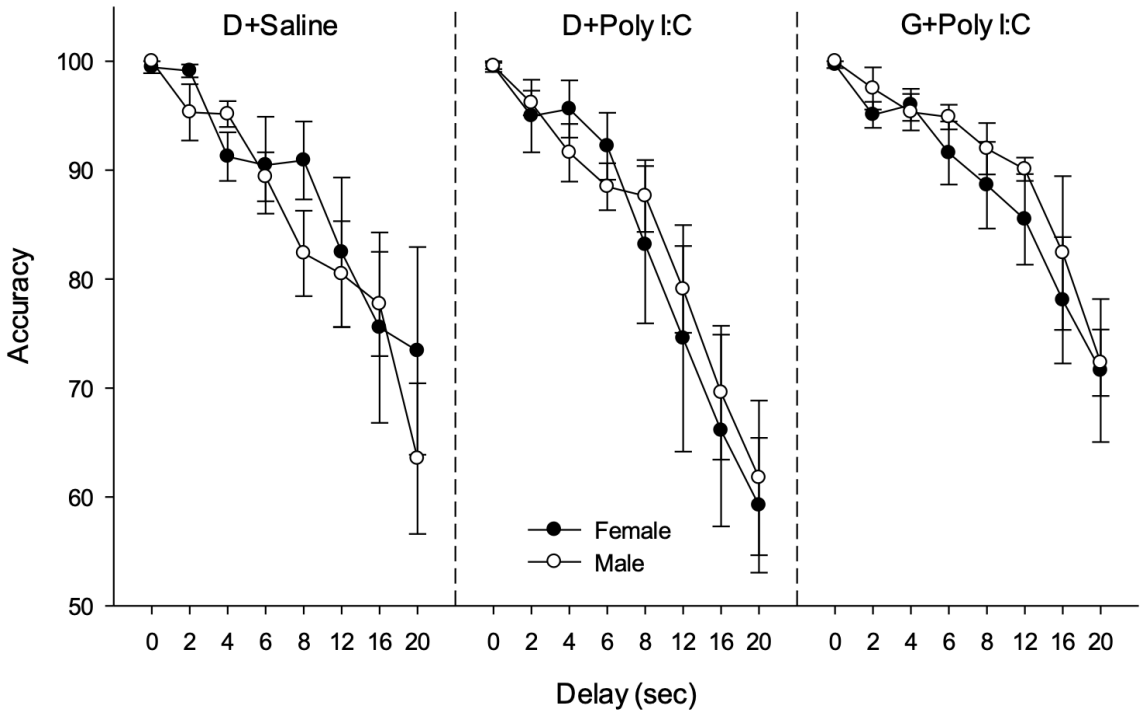

D+Saline
D+Poly I:C
G+Poly I:C
Accuracy
100
90
80
70
60
50
0 2 4 6 8 12 16 20
Female
Male
Delay (sec)

Figure 10.

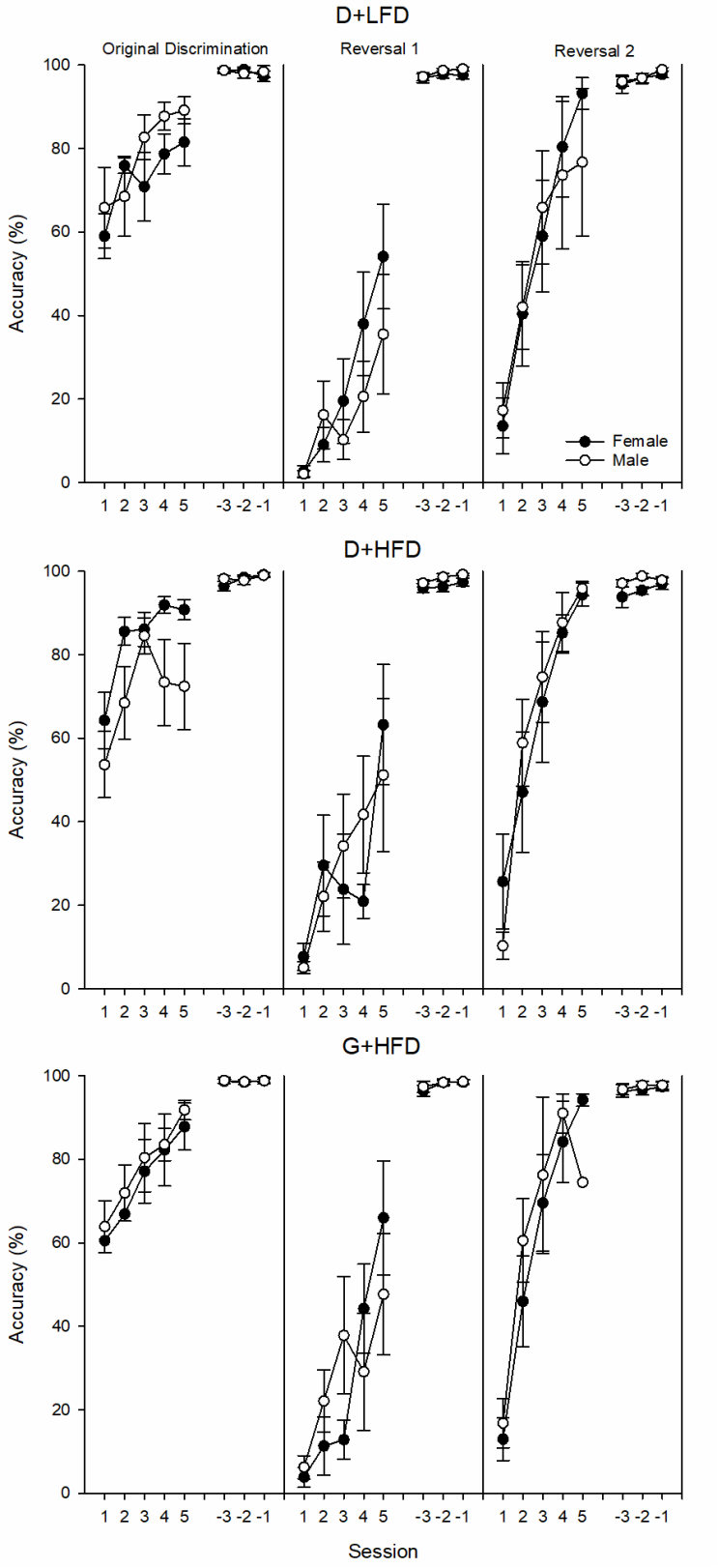

D+LFD
Original Discrimination
Reversal 1
Reversal 2
Accuracy (%)
Female
Male
D+HFD
G+HFD
Session

Figure 11.

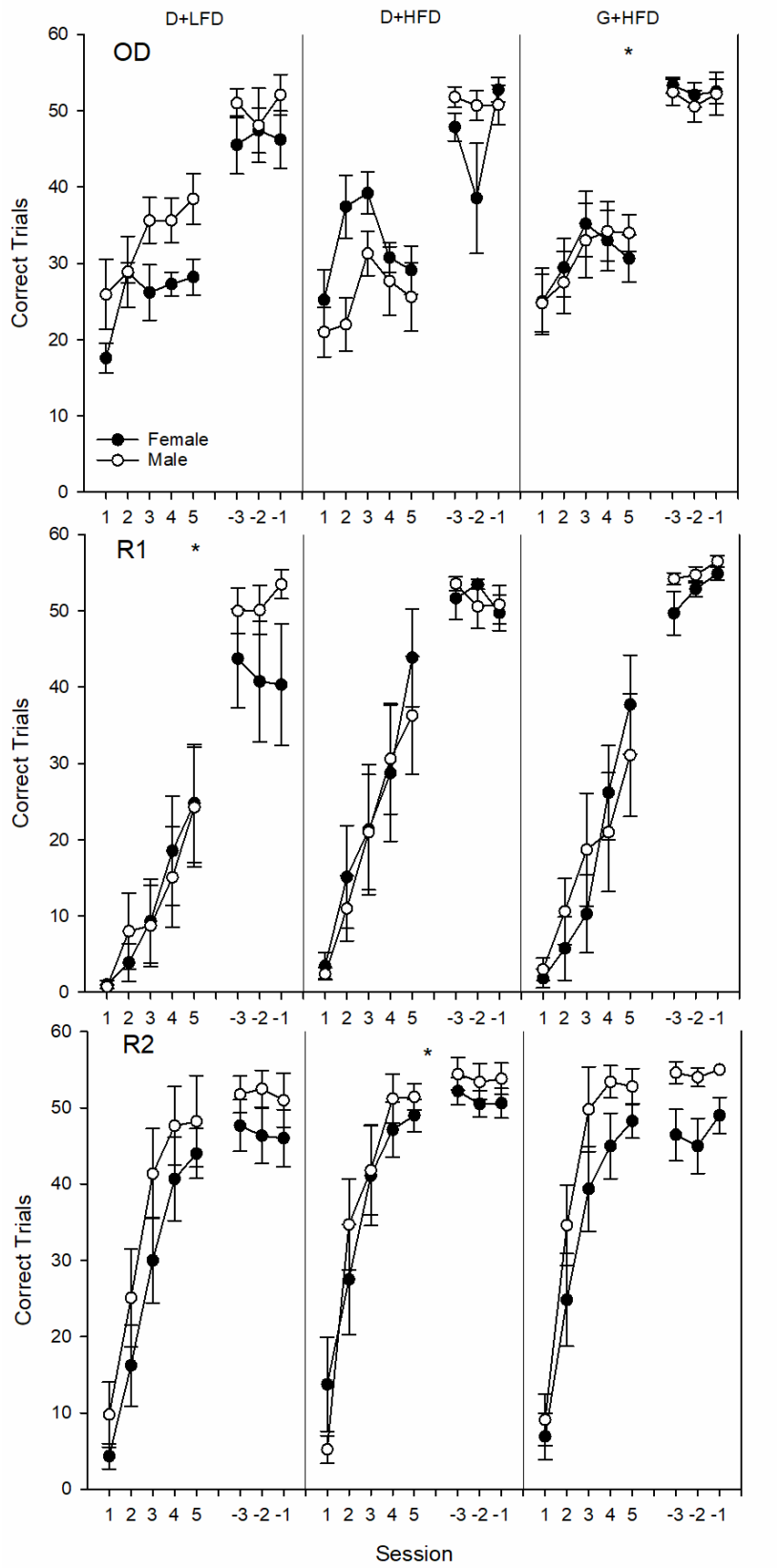

D+LFD
D+HFD
G+HFD
OD
R1
R2
*
Correct Trials
Female
Male
Session
1 2 3 4 5 -3 -2 -1
0 10 20 30 40 50 60

Figure 12.

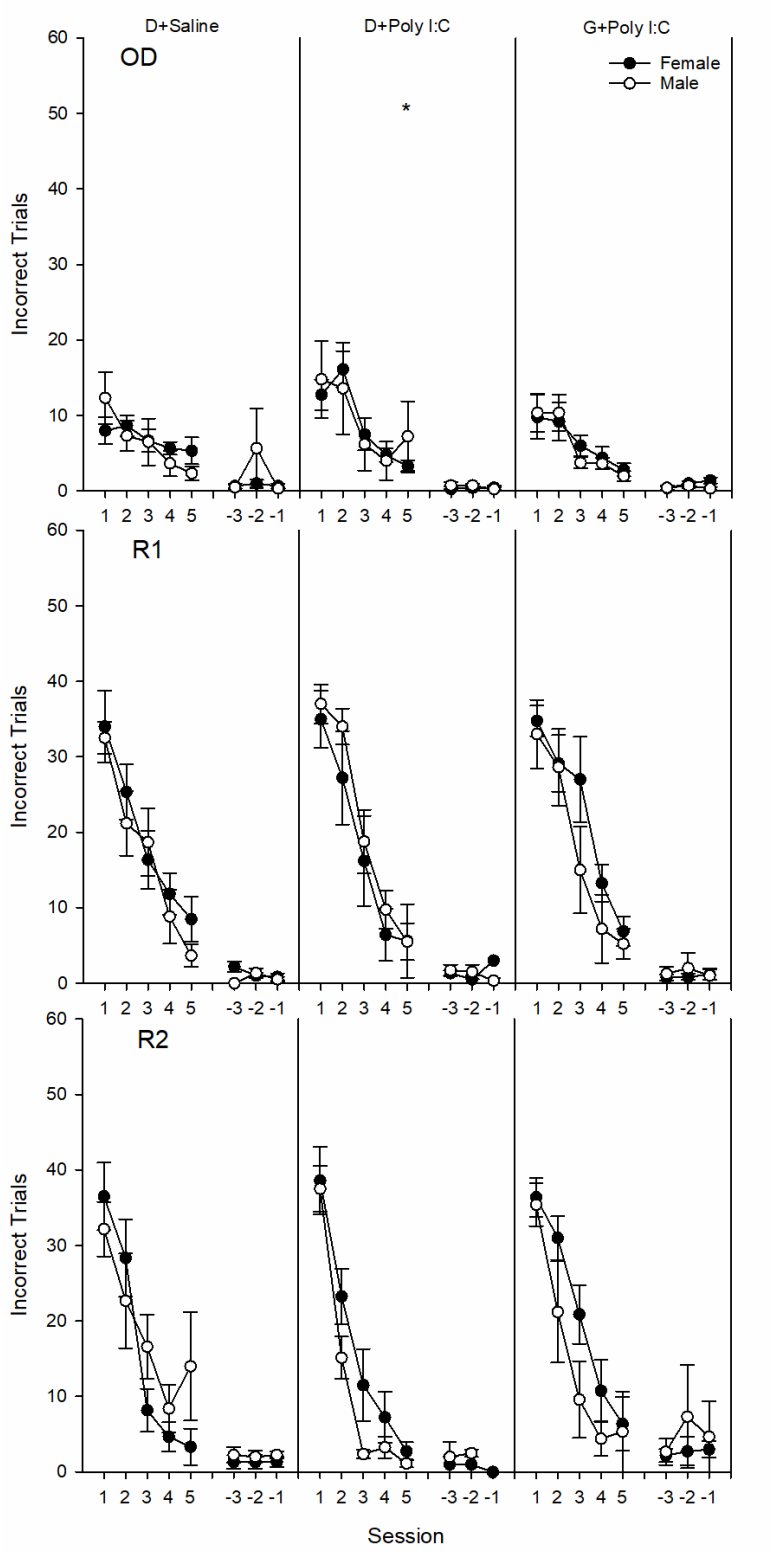

D+Saline
D+Poly I:C
G+Poly I:C
OD
R1
R2
Female
Male
*
Incorrect Trials
Session

Figure 13.

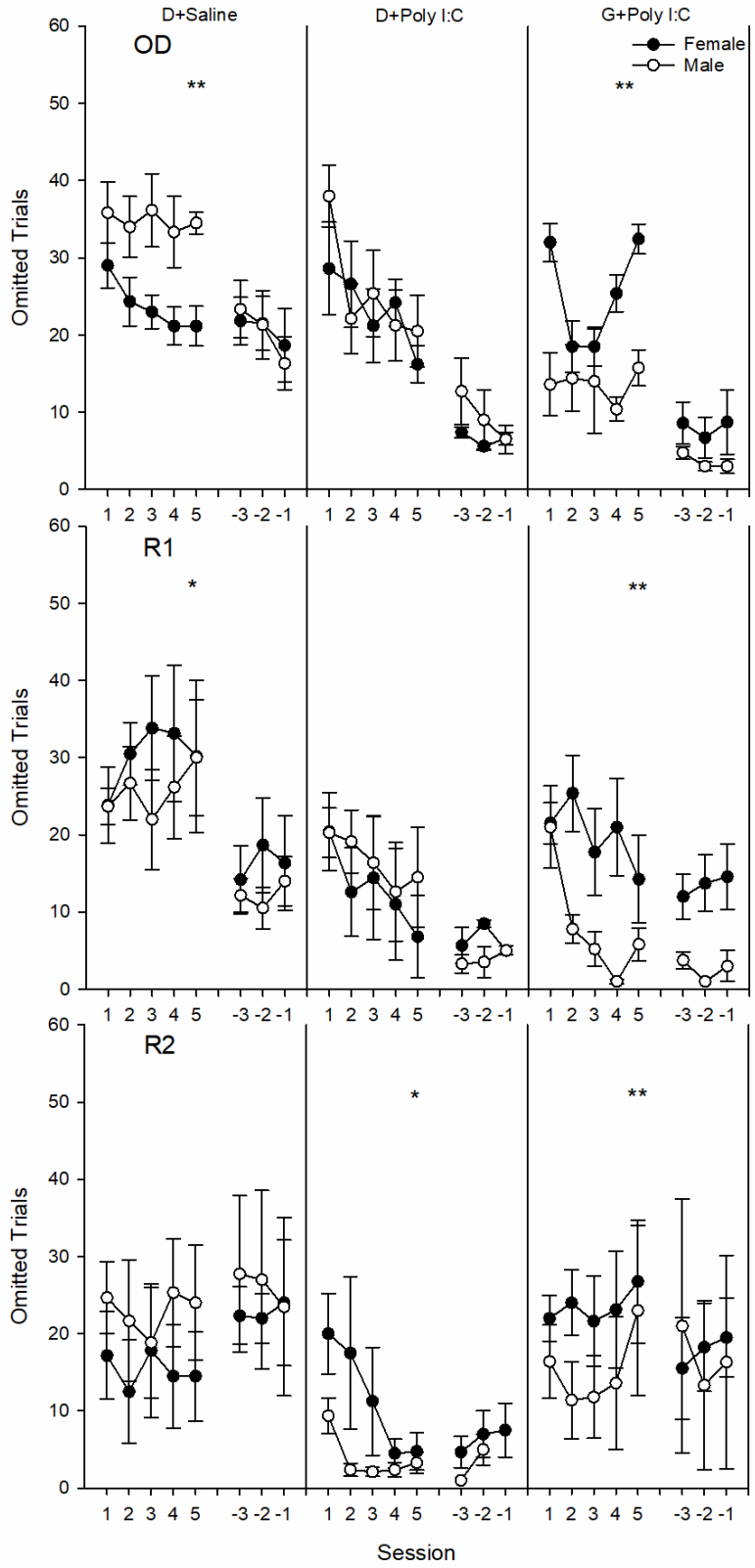

D+Saline
D+Poly I:C
G+Poly I:C
Female
Male
OD
R1
R2
**
*
Omitted Trials
Session
0
10
20
30
40
50
60
1 2 3 4 5 -3 -2 -1

Figure 14.

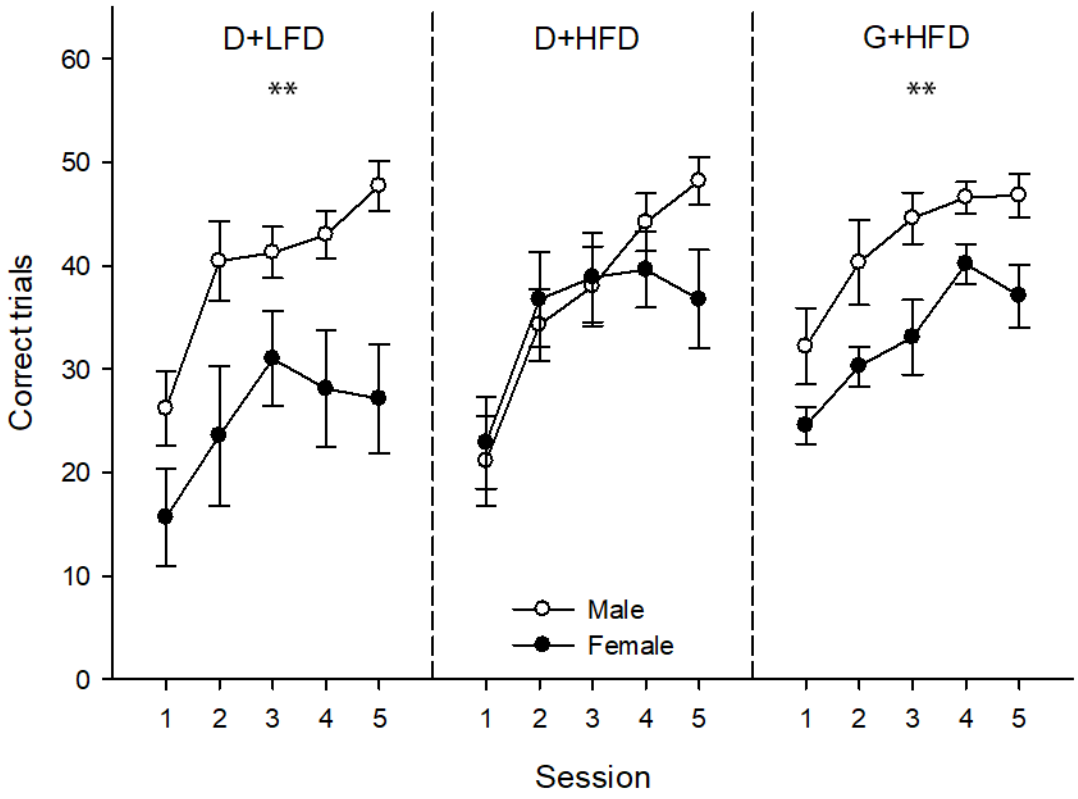

D+LFD
**
D+HFD
G+HFD
**
Correct trials
60
50
40
30
20
10
0
Male
Female
1
2
3
4
5
Session

Figure 15.

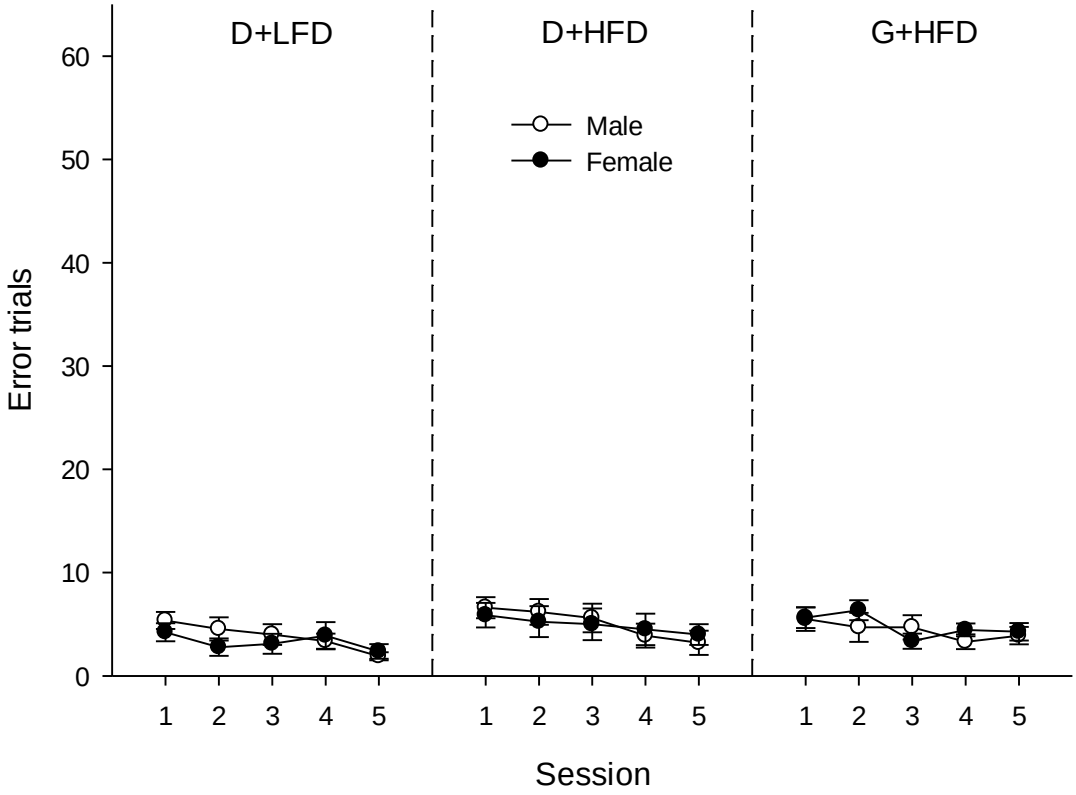

D+LFD
D+HFD
G+HFD
Male
Female
Error trials
0
10
20
30
40
50
60
1
2
3
4
5
Session

Figure 16.

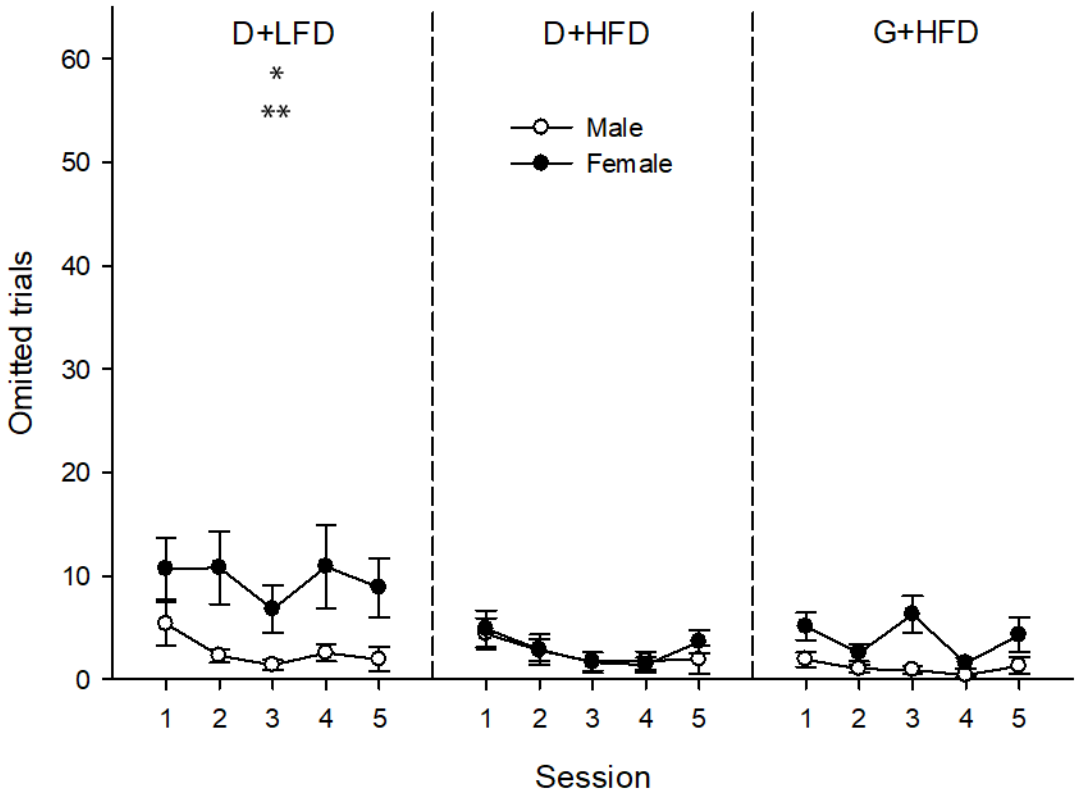

D+LFD
D+HFD
G+HFD
*
**
Male
Female
Omitted trials
60
50
40
30
20
10
0
1
2
3
4
5
Session

Figure 17.

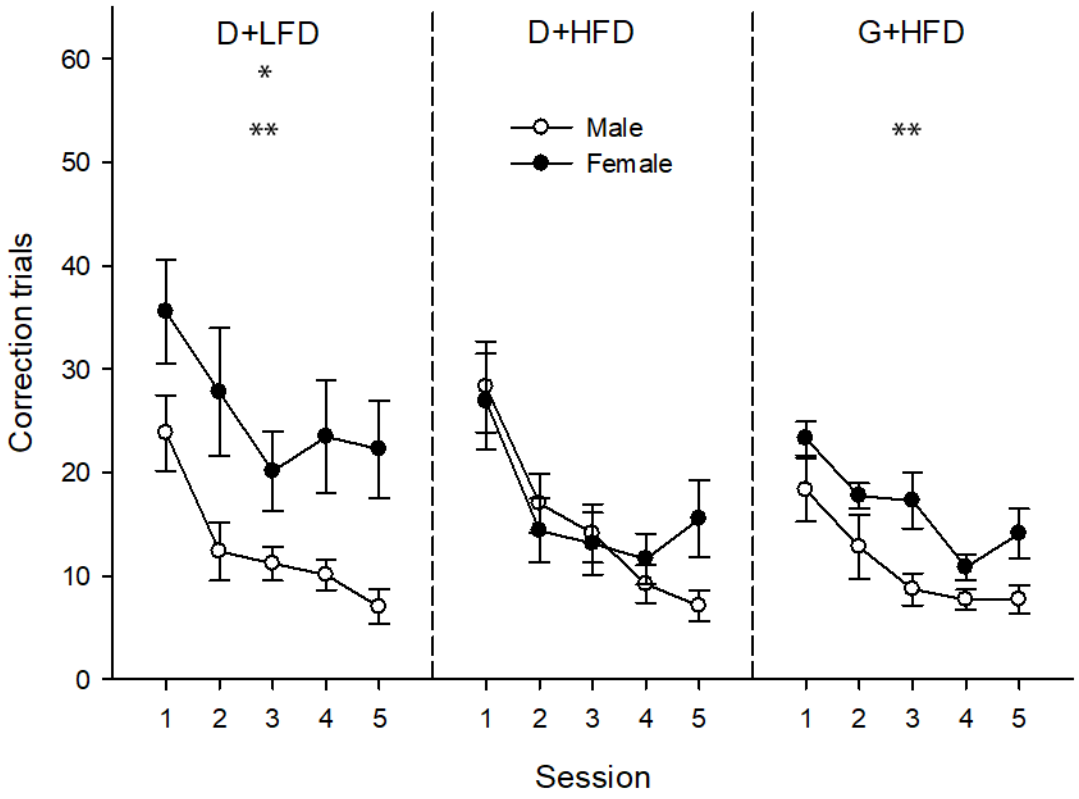
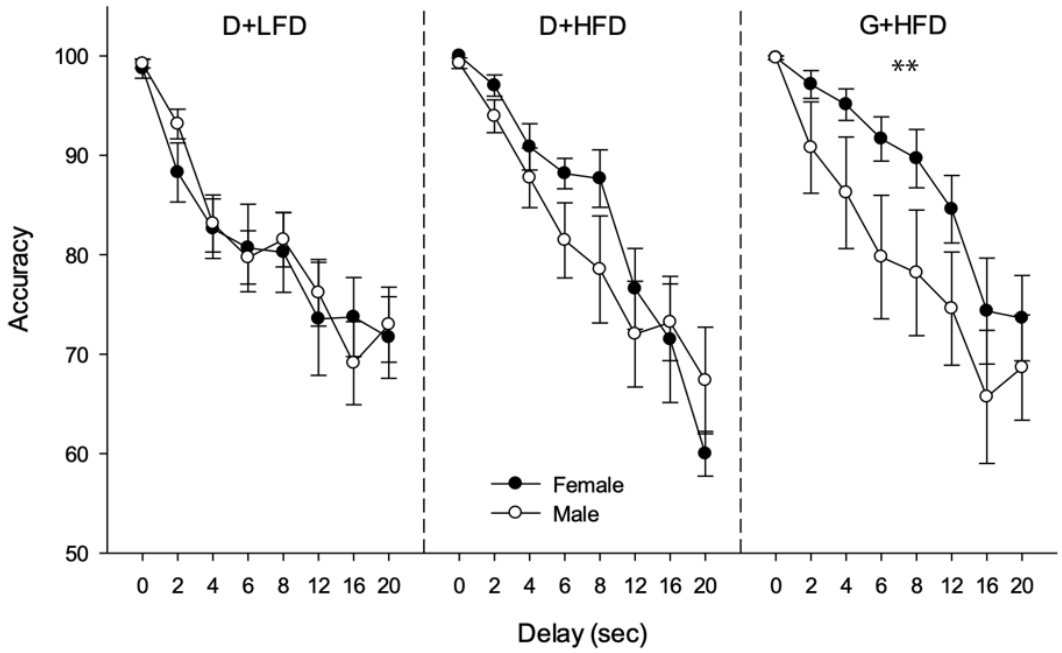

D+LFD
D+HFD
G+HFD
*
**
**
Male
Female
Correction trials
Session
0
10
20
30
40
50
60
1
2
3
4
5

Figure 18.


D+LFD
D+HFD
G+HFD
**
Accuracy
100
90
80
70
60
50
0 2 4 6 8 12 16 20
Female
Male
Delay (sec)

Appendix B
Figure Captions

Figure 1. Intradimensional Shifting for Acute Inflammation experiment. Mean (± SEM) percent accuracy across the first five and last three sessions of each experimental phase, which is indicated by a break in data. The three experimental phases are original discrimination (left), reversal 1 (center), and reversal 2 (right). Data are represented separately for exposure (D+Saline, top; D+Poly I:C, middle; G+Poly I:C, bottom) and sex (Female, closed circle; Male, open circle). Accuracy is only calculated for trials on which animals responded (correct trials / (correct trials + incorrect trials).

Figure 2. Intradimensional Shifting for Acute Inflammation experiment. Mean (± SEM) correct trials across the first five and last three sessions of each experimental phase, which is indicated by a break in data. The three phases represented are original discrimination (top), Reversal 1 (middle), and Reversal 2 (bottom). Data are presented separately for exposure (D+Saline, left; D+Poly I:C, center; and G+Poly I:C, right) and sex (Female, closed circle; Male, open circle). * significant exposure difference. ** significant sex difference.

Figure 3. Intradimensional Shifting for Acute Inflammation experiment. Mean (± SEM) error trials across the first five and last three sessions of each experimental phase, which is indicated by a break in data. The three phases of the intradimensional shift are original discrimination (top), Reversal 1 (middle), and Reversal 2 (bottom). Data are presented separately for exposure (D+Saline, left; D+Poly I:C, center; and G+Poly I:C, right) and sex (Female, closed circle; Male, open circle). * significant exposure difference. ** significant sex difference.

Figure 4. Intradimensional Shifting for Acute Inflammation experiment. Mean (± SEM) omitted trials across the first five and last three sessions of each experimental phase, which is indicated by a break in data. The three phases of the intradimensional shift are original discrimination (top), Reversal 1 (middle), and Reversal 2 (bottom). Data are presented separately for exposure (D+Saline, left; D+Poly I:C, center; and G+Poly I:C, right) and sex (Female, closed circle; Male, open circle). * significant exposure difference. ** significant sex difference.

Figure 5. Extradimensional Shifting for Acute Inflammation experiment. Mean (± SEM) correct trials across the first five sessions of the visual discrimination. Data are presented separately for exposure (D+Saline, left; D+Poly I:C, center; and G+Poly I:C, right) and sex (Female, closed square; Male, open triangle). * significant exposure difference. ** significant sex difference.

Figure 6. Extradimensional Shifting for Acute Inflammation experiment. Mean (± SEM) error trials across the first five sessions of the visual discrimination. Data are presented separately for exposure (D+Saline, left; D+Poly I:C, center; and G+Poly I:C, right) and sex (Female, closed square; Male, open triangle). * significant exposure difference. ** significant sex difference.

Figure 7. Extradimensional Shifting for Acute Inflammation experiment. Mean (± SEM) omitted trials across the first five sessions of the visual discrimination. Data are presented

separately for exposure (D+Saline, left; D+Poly I:C, center; and G+Poly I:C, right) and sex (Female, closed square; Male, open triangle). * significant exposure difference. ** significant sex difference.

Figure 8. Extradimensional Shifting for Acute Inflammation experiment. Mean (± SEM) correction trials across the first five trials of the visual discrimination. Data are presented separately for exposure (D+Saline, left; D+Poly I:C, center; and G+Poly I:C, right) and sex (Female, closed square; Male, open triangle). * significant exposure difference. ** significant sex difference.

Figure 9. Working Memory for Acute Inflammation experiment. Mean (± SEM) accuracy as a function of delay (0.01, 2, 4, 6, 8, 12, 16, 20s) for male (open circle) and female (closed circle) mice in the three exposures: D+Saline (left), D+Poly I:C (center), and G+Poly I:C (right). * significant exposure difference. ** significant sex difference.

Figure 10. Intradimensional Shifting for Chronic Inflammation experiment. Mean (± SEM) percent accuracy across the first five and last three sessions of each experimental phase, which is indicated by a break in data. The three experimental phases are original discrimination (left), reversal 1 (center), and reversal 2 (right). Data are represented separately for exposure (D+LFD, top; D+HFD, middle; G+HFD, bottom) and sex (Female, closed circle; Male, open circle). Accuracy is only calculated for trials on which animals responded (correct trials / (correct trials + incorrect trials).

Figure 11. Intradimensional Shifting for Chronic Inflammation experiment. Mean (± SEM) correct trials across the first five and last three sessions of original discrimination (top), Reversal 1 (middle), and Reversal 2 (bottom). Data are presented separately for exposure (D+LFD, left; D+HFD, center; and G+HFD, right) and sex (Female, closed circle; Male, open circle). * significant exposure difference. ** significant sex difference.

Figure 12. Intradimensional Shifting for Chronic Inflammation experiment. Mean (± SEM) error trials across the first five and last three sessions of original discrimination (top), Reversal 1 (middle), and Reversal 2 (bottom). Data are presented separately for exposure (D+LFD, left; D+HFD, center; and G+HFD, right) and sex (Female, closed circle; Male, open circle). * significant exposure difference. ** significant sex difference.

Figure 13. Intradimensional Shifting for Chronic Inflammation experiment. Mean (± SEM) omitted trials across the first five and last three sessions of original discrimination (top), Reversal 1 (middle), and Reversal 2 (bottom). Data are presented separately for exposure (D+LFD, left; D+HFD, center; and G+HFD, right) and sex (Female, closed circle; Male, open circle). * significant exposure difference. ** significant sex difference.

Figure 14. Extradimensional Shifting for Chronic Inflammation experiment. Mean (± SEM) correct trials across the first five trials of the visual discrimination. Data are presented separately for exposure (D+LFD, left; D+HFD, center; and G+HFD, right) and sex (Female, closed circle; Male, open circle). * significant exposure difference. ** significant sex difference.

Figure 15. Extradimensional Shifting for Chronic Inflammation experiment. Mean (± SEM) error trials across the first five trials of the visual discrimination. Data are presented

separately for exposure (D+LFD, left; D+HFD, center; and G+HFD, right) and sex (Female, closed circle; Male, open circle). * significant exposure difference. ** significant sex difference.

Figure 16. Extradimensional Shifting for Chronic Inflammation experiment. Mean (± SEM) omitted trials across the first five trials of the visual discrimination. Data are presented separately for exposure (D+LFD, left; D+HFD, center; and G+HFD, right) and sex (Female, closed circle; Male, open circle). * significant exposure difference. ** significant sex difference.

Figure 17. Extradimensional Shifting for Chronic Inflammation experiment. Mean (± SEM) correction trials across the first five trials of the visual discrimination. Data are presented separately for exposure (D+LFD, left; D+HFD, center; and G+HFD, right) and sex (Female, closed circle; Male, open circle). * significant exposure difference. ** significant sex difference.

Figure 18. Working Memory for Chronic Inflammation experiment. Mean (± SEM) accuracy as a function of delay (0.01, 2, 4, 6 8, 12, 16, 20s) for male (open circle) and female (closed circle) mice in the three exposures: D+LFD (left), D+HFD (center), and G+HFD (right). * significant exposure difference. ** significant sex difference.

Appendix C

Table 1.

Exposure	Sex	Original Discrimination		Reversal 1		Reversal 2	
		Accuracy 1	Accuracy 2	Accuracy 1	Accuracy 2	Accuracy 1	Accuracy 2
D+Saline	F	0%	100%	33%	100%	50%	100%
	M	17%	100%	50%	100%	17%	100%
D+Poly I:C	F	100%	100%	100%	100%	20%	100%
	M	63%	100%	100%	100%	100%	100%
G+Poly I:C	F	71%	100%	100%	100%	57%	100%
	M	100%	100%	100%	100%	80%	100%

Table 2

Exposure	Sex	Original Discrimination		Reversal 1		Reversal 2	
		Accuracy 1	Accuracy 2	Accuracy 1	Accuracy 2	Accuracy 1	Accuracy 2
D+LFD	F	33%	100%	44%	100%	33%	100%
	M	55%	100%	64%	100%	73%	100%
D+HFD	F	44%	100%	67%	100%	56%	100%
	M	50%	100%	80%	100%	80%	100%
G+HFD	F	73%	100%	82%	100%	46%	100%
	M	50%	100%	100%	100%	100%	100%

Appendix D
Table Captions

Table 1. Acute Inflammation: Percent animals meeting accuracy criteria in Intradimensional Shift. The table shows the percentage of animals in each exposure by sex group for both of the accuracy criteria used in the study. Accuracy 1 refers to the original criteria that required 85% accuracy for three consecutive sessions (51 of 60 trials were correct). Accuracy 2 refers to the that satisfied the modified contingency, which required 85% accuracy for trials on which the animals responded; omissions were excluded from calculations.

Table 2. Chronic Inflammation: Percent animals meeting accuracy criteria in Intradimensional shift. The table shows the percentage of animals in each exposure by sex group for both of the accuracy criteria used in the study. Accuracy 1 refers to the original criteria that required 85% accuracy for three consecutive sessions (51 of 60 trials were correct). Accuracy 2 refers to the that satisfied the modified contingency, which required 85% accuracy for trials on which the animals responded; omissions were excluded from calculations.

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