The role of maternal immune activation in altering the neurodevelopmental trajectories of offspring: a translational review of neuroimaging studies with implications for autism spectrum disorder and schizophrenia

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Abstract

Exposure to maternal infection *in utero* increases the risk that offspring will develop neurodevelopmental disorders such as autism spectrum disorder (ASD) and schizophrenia. Research in animal models has confirmed this link and demonstrated that maternal immune activation (MIA) is sufficient to induce alterations in offspring neurodevelopment. Building homology between observations made in humans and animal models is a challenge; however, neuroimaging allows for homologous characterization of developmental trajectories across species. This systematic review aims to discuss findings from human and animal studies that performed neuroimaging in offspring exposed to maternal infection, inflammation, or MIA, in the context of neurodevelopmental disorders.

1. Introduction

Epidemiological evidence has established a relationship between *in utero* exposure to maternal infection and increased risk of developing neurodevelopmental disorders such as schizophrenia and autism spectrum disorder (ASD) later in life (Brown et al. 2004; Selten et al. 2010; Brown et al. 2001; Wright et al. 1995). Although primarily associated with ASD and schizophrenia, there have been less frequent associations with other neurodevelopmental disorders, such as attention deficit/hyperactivity disorder, cerebral palsy, and epilepsy (Knuesel et al. 2014). One of the first observations of this association dates back to the 1918 Spanish influenza pandemic, in which Karl A. Menninger documented an association between patients with psychotic disorders and exposure to maternal influenza (Yudofsky 2009). Further, after the 1964 rubella pandemic, the prevalence of schizophrenia and ASD rose from the expected ~1% to 20% and 13%, respectively, in affected areas (Estes and McAllister 2016a; Qi Li et al. 2009).

Interestingly, the link between prenatal exposure to infection and increased risk for neurodevelopmental disorders is not pathogen specific; there is evidence for exposure to *Toxoplasma Gondii* (Preben Bo Mortensen, Nørgaard-Pedersen, Waltoft, Sørensen, Hougaard, Torrey, et al. 2007; Preben Bo Mortensen, Nørgaard-Pedersen, Waltoft, Sørensen, Hougaard, and Yolken 2007; Pedersen et al. 2011; Severance et al. 2016), reproductive, genital, and urinary tract infections (Clarke et al. 2009; Nielsen, Laursen, and Mortensen 2013), herpes simplex virus 2 (S. L. Buka et al. 2003; Stephen L. Buka et al. 2008; S. L. Buka et al. 2001; Preben B. Mortensen et

al. 2010), pneumonia, and others as potent risk factors. Common to this diverse group of pathogens is the activation of the maternal immune system and increased maternal serum levels of pro-inflammatory cytokines such as interleukin (IL)-6, IL-1β, and tumor necrosis factor (TNF)-α (Miller et al. 2011; Potvin et al. 2008; Masi et al. 2015; Ricci et al. 2013; Molloy et al. 2006; Al-Asmari and Khan 2014).

Animal research is an essential tool for understanding neurodevelopment and developing new diagnostic tools and therapeutics. This is especially important given the challenges of studying maternal immune activation (MIA) in humans. Animal models have established causality by showing that MIA during pregnancy does disrupt early neurodevelopment of offspring, altering their developmental trajectories. Long-term behavioural, structural, and functional deficits relevant to schizophrenia and ASD are commonly observed in these offspring, including altered cognitive and social behaviour, impaired sensorimotor gating, and increased anxiety, as well as altered cell migration, microglial function, synaptic structure, and function (as reviewed in (Gumusoglu and Stevens 2019; Reisinger et al. 2015; Estes and McAllister 2016b; Knuesel et al. 2014; Boksa 2010)). These structural and functional alterations do not seem to depend on specific immune-activating agents; however, certain cytokines, such as IL-6 and IL-17a, have been identified as key players (Gumusoglu and Stevens 2019; Smolders et al. 2018; Choi et al. 2016; W.-L. Wu et al. 2017; Bergdolt and Dunaevsky 2019). Based on the idea that increased maternal cytokine levels and not specific pathogens disrupt neurodevelopment of the offspring, the two most commonly used immune activators are are lipopolysaccharide (LPS), a gram-negative bacterial cell wall component that mimics a bacterial infection by binding to toll like receptor (TLR)4, and polyriboinosinic polyribocytidylic acid (poly I:C), a synthetic double stranded RNA analog that mimics a viral infection by binding to TLR3 (Dowling and Mansell 2016).

Despite many important efforts, there are still significant gaps in our knowledge regarding the precise mechanism by which prenatal MIA disrupts early brain development; further, the differential impact on neurodevelopmental trajectories of dose and timing of immunogens used to induce MIA remains elusive (Kentner et al. 2019; Estes and McAllister 2016a). The hemochorial placenta (occuring in mammals including humans and rodents) allows for direct contact between maternal and fetal compartments (Colucci et al. 2011). This suggests that maternal cytokines and chemokines may cross the placenta and enter the fetal compartment in the event of an immune challenge. The fetal immune system may not have the capacity to adequately respond to elevated

levels of proinflammatory cytokines, which may disrupt the cytokine equilibrium and negatively impact fetal brain development (Reisinger et al. 2015). Microglia, the resident immune cells of the central nervous system, are thought to be central in the MIA-induced neurodevelopmental disruptions given their regulatory role in pruning and maintenance of synapses, and evidence of their disruption in both schizophrenia and ASD (Smolders et al. 2018).

We are faced with a consistent problem across neuroscientific disciplines, specifically in the neurodevelopmental field, regarding how to build a homology between observations made in humans and animal models of neuropsychiatric disorders. Some of this difficulty stems from the limited assays that can be used to examine neurodevelopmental trajectories across species. Neuroimaging techniques (e.g. magnetic resonance imaging [MRI], positron emission tomography [PET]) are an intriguing exception in that they allow for neuroanatomical specificity and further lend themselves to longitudinal data acquisition and analyses that allow for examination of the nature and timing of the emergence of aberrant neurodevelopment. This type of work has been critical in furthering our understanding of normative brain development in both humans and animals (Hammelrath et al. 2016; Mengler et al. 2014; Raznahan et al. 2014; Giedd 2010; Reardon et al. 2018; Qiu et al. 2018), and of neurodevelopmental disorders in humans, and has led to the idea that these disorders are characterized by deviation from normative developmental trajectories (Shaw et al. 2008, 2013, 2014; Raznahan et al. 2014).

2. Methods

2.1. Literature Search

Embase, Medline, and PsycINFO were used to search for published English-language human and animal studies using neuroimaging modalities to investigate the effects of prenatal MIA on offspring. The following search terms were used in Ovid: ("magnetic resonance imaging" or “MRI” or "functional magnetic resonance imaging" or "fMRI" or "positron emission tomography" or "PET" or "magnetic resonance spectroscopy" or "MRS" or "diffusion tensor imaging" or "DTI" or "Computed Tomography" or "CT") AND ("prenatal maternal immune activation" or "MIA" or "maternal infection" or "maternal inflammation" or "prenatal immune challenge"). Two authors (E.G. and E.P.) performed the search independently (last search:

October 2018) and evaluated eligibility for inclusion based on titles and abstracts of all publications. Authors also reviewed reference sections of major reviews (Reisinger et al. 2015; Meyer 2014).

2.2. Inclusion Criteria

Full-length English language articles were included if: (1) the study investigated effects of exposure prenatal MIA on offspring development (animal or human) and (2) used an imaging modality to assay the brain.

2.3. Exclusion Criteria

Case studies were excluded.

3. Results

The primary Ovid search resulted in 645 publications (871 prior to removing duplicates). Fifty-four articles were selected to undergo a full-text assessment for eligibility. Twenty-nine animal studies (Kannan et al. 2007; Saadani-Makki et al. 2009; Kannan, Saadani-Makki, Balakrishnan, Chakraborty, et al. 2011; Kannan, Saadani-Makki, Balakrishnan, Dai, et al. 2011; Z. Zhang et al. 2018; Fatemi et al. 2008; Fatemi, Folsom, Reutiman, Abu-Odeh, et al. 2009; Fatemi, Folsom, Reutiman, Huang, et al. 2009; Qi Li et al. 2009, 2010; Q. Li et al. 2015; Piontkewitz, Assaf, and Weiner 2009; Piontkewitz, Arad, and Weiner 2011b, [a] 2011; Short et al. 2010; Willette et al. 2011; Girard et al. 2010; Beloosesky et al. 2013; Bergeron et al. 2013; Malkova et al. 2014; Arsenault et al. 2014; Vernon et al. 2015; Richetto et al. 2017; Crum et al. 2017; da Silveira et al. 2017; Ginsberg et al. 2017; Sharabi et al. 2018; Ooi et al. 2017; Bauman et al. 2013) and 10 human studies (Ellman et al. 2010; Graham et al. 2018; Rudolph et al. 2018; Rasmussen et al. 2018; Spann et al. 2018; Dhombres et al. 2017; Jenster et al. 2018; Birnbaum et al. 2017; Lipitz et al. 2010; Diebler, Dusser, and Dulac 1985) were deemed eligible for inclusion. The characteristics of the animal and human studies are reported in **Tables 1** and **2**, respectively.

Table 1. Summary of human studies that met inclusion criteria (n=10)

Study number *	Authors, journal, year	Offspring n, sex	Mean age (+/- SD)	Study Population	Design of brain imaging acquisition	Measure of maternal inflammation	Gestational timing	Neuro-imaging	Key MRI findings
1	Rudolph et al. (2018), *Nature Neuroscience*	84 (50% M)	3.97 weeks (+/- 1.84)	Healthy mothers' infants	CS	Maternal serum IL-6	All trimesters averaged	rs-fMRI & T1- and T2-weighted sMR (3T); resolution for rs-fMRI=NA, for T1=1x1x1mm^3, for T2=1x1x1mm^3	Maternal IL-6 concentration associated with: ● SUB, DAN, SAL, CER, VAN, VIS, cingulopercular, and frontoparietal network connectivity ● Connectivity between SUB-CER, VIS-DAN, SAL-CON ● Meta-analysis defined WM fMRI mask ● Prediction of within-network SAL connectivity and between-network connectivity in DAN, VAN, SAL, SUB
2	Spann et al. (2018), *The Journal of Neuroscience*	72 (36 after QC; 66.7% M)	~42 weeks (mean +/- 1.9 weeks)	Nulliparous pregnant adolescent women's offspring (healthy)	CS	Maternal serum IL-6 and CRP	Third trimester (34-37 weeks)	rs-fMRI & T2-weighted sMR (3T); resolution for rs-fMRI=3.16x3.16x5mm^3, for T2=1x1x1mm^3	● Higher maternal IL-6 concentration associated with stronger left insula mPFC and lateral occipital gyrus connectivity, weaker connectivity between dACC and dorsomedial PFC; ● Higher maternal CRP levels associated with greater connectivity between left insula and right temporoparietal junction, right insula and basal ganglia, dACC and cuneus, temperoparietal junction and extrastriate cortices, and weaker connectivity between dACC and dmPFC and right basal ganglia
3	Birnbaum R et al. (2017), *Prenatal Diagnosis*	81	32-33 weeks of gestation	Fetuses of women positive for CMV	CS	Maternal seroconversion for CMV	1st, 2nd, and 3rd trimesters	T2-weighted sMRI (1.5T); resolution=0.625x1.46x3-5mm^3	● Bilateral temporal cavitations ● Unilateral dilatation of right temporal horn ● Periventricular WM hyperintense signal (33 weeks) ● Subcortical hyperintense at 29 weeks improved by 33 weeks
4	Graham AM et al. (2017), *Biological Psychiatry*	86 sMRI, 70 fMRI (59.3% M)	3.97 (+/- 1.84) weeks	Healthy mothers' infants	CS	Maternal serum IL-6	All trimesters averaged	T1- and T2-weighted sMRI & fMRI (3T); resolution for	Higher maternal IL-6 associated with: ● Larger right (not left) amygdala volume and amygdala connectivity ● Stronger connectivity between right amygdala and right anterior insula,

								T1=1x1x1mm^3, for T2=1x1x1mm^3, for fMRI=NA	fusiform gyrus/inferior temporal gyrus, caudate, and thalamus, left brainstem and weaker connectivity to left superior occipital gyrus; ● Stronger connectivity between left amygdala and right fusiform/ITG, pareital/somatosensory cortex, parahippocampl gyrus, and weaker connectivity to ITG
5	Rasmussen et al. (2017), *NeuroImage*	32 (55.8% M)	34.6-41.8 weeks (scan 1); 51.3-56.1 weeks (scan 2)	Healthy mothers' infants	LG	Maternal serum IL-6	All trimesters averaged	T1- and T2-weighted sMRI & DTI (3T); resolution for T1=1x1x1mm^3, for T2=1x1x1mm^3, for DTI=2x2x2mm^3, 42 encoding directions	● Higher maternal IL-6 concentration associated with lower UF FA at birth with no association at 12 months indicative of stronger increase in FA from 1-12 months of age
6	Dhombres F et al. (2015), *Fetal Diagnosis and Therapy*	10	23-34 weeks of gestation	Fetuses exposed to T. gondii	CS	Serum IgG and T. gondii in amniotic fluid	All trimesters averaged	T1- and T2-weighted sMRI (1.5T); resolution for T1=1.25x2.56x4 mm^3, for T2=1.25x1.88x4 mm^3	● Abnormal echogenicity and thickness of germinal matrix ● Fetal brain lesions in white matter of subcortical, periaqueductal and periventricular regions at 33 weeks ● Lesions of necrosis in periventricular WM surrounded by inflammatory lesions and calcifications
7	Jenster M et al. (2013), *International Pediatric Research Foundation*	42 (61% M) chorioamnionitis, 29 (48% M) neonatal sepsis, 193 (55% M) no infection	5 days of life	Offspring exposed to chorioamnionitis or neonatal sepsis	CS	Maternal or neonatal fever, uterine tenderness, maternal or fetal tachycadia, purulent amniotic fluid or vaginal dischargne, maternal leukocytosis, histological	NA	T1- and T2-weighted sMRI & DWI (1.5T); resolution for T1=0.7x0.7x1mm^3, T2=0.92x0.7x4mm^3, DTI=1.4	● Watershed pattern of injury seen in 98 subjects ● 59 subjects with basal ganglia/thalamus patterns of damage ● Neonatal sepsis associated with more severe damage; maternal chorioamnionitis was associated with moderate-severe brain injury

						chorioamnionitis, neonatal sepsis, positive blood culture for pathogenic species, low white blood cell count, low absolute neutrophil count		x1.4x3mm^3, 3, 6 or 30 encoding directions	
8	Ellman LM et al. (2010), *Schizophrenia Research*	SSD 17 (70% M), CTL 8 (75% M)	SSD = 39.96 (1.78) Control = 41.17 (1.69)	Schizophrenia spectrum disorder (from large birth cohort study)	CS	Maternal serum IL-8	2nd, 3rd trimesters	T1-weighted sMRI (1.5T); resolution=1x1x1.4mm^3	● Maternal IL-8 associated with increases in ventricular volume, decreased entorhinal cortex volumes and posterior cingulate in SSD individuals
9	Lipitz S et al (2010), *Ultrasound Obstet Gynecol*	10 1st semester, 19 2nd trimester, 9 3rd trimester	30 weeks gestation (1st & 2nd trimester infections), later for 3rd trimester infections	Fetuses of women positive for CMV	CS	Maternal serum IgG and IgM in the amniotic fluid	1st, 2nd, and 3rd trimesters	T1- and T2-weighted sMRI & DWI (1.5T); resolution for T1=0.75-0.93x1-1.3x3-4mm^3, for T2=1.7x1.25x4mm^3, for DTI=1.7x1.25x4mm^3, encoding direction NA	● CMV associated with frontal, temporal, and parietal lobe, right caudate nucleus hyperintensities;
10	Diebler at el. (1985), *Neuroradiology*	31	0-2 months (n=17), 2-12 months(n=8); 1-2 years (n=6)	Infants and children exposed to T. gondii	CS	Maternal or infantile serology and or parasitological examination of placenta; significant elevation of antitoxoplasma titers	2nd, 3rd trimesters	CT scan, no resolution reported	● Toxoplasmosis associated with hydrocephalous, hemiplegia and diplegia, calcifications in the basal ganglia and periventricular WM, porencephalic cysts and multicystic encephalomalacia ● Early infection (<20 weeks): ventricular dilatation, porencephalic cysts and extensive calcifications particularly in the basal ganglia. ● Infection between 20 and 30 weeks resulted in extensive periventricular

									calcifications and ventricular dilatation. ● Late infection (<30th week) associated with fewer periventricular and intracerebral

CER: cerebellar network, CS: cross sectional, CMV: cytomegalovirus, CT: computed tomography, dACC: dorsal anterior cingulate, DAN: dorsal attention network, dmPFC: dorsomedial prefrontal cortex, DTI: diffusion tensor imaging, DWI: diffusion weighted imaging, IL: interleukin, ITG: inferior temporal gyrus, LG: longitudinal, rs-fMRI: resting state functional magnetic resonance imaging, SAL: salience network, sMRI: structural magnetic resonance imaging, SSD: schizophrenia spectrum disorder, SUB: subcortical network, T: Tesla, VAN: ventral attention network, VIS: visual network, WM: white matter

Table 2. Summary of preclinical studies that met inclusion criteria (n=29)

Study number *	**Author, year, journal**	**Species, Strain, Sex**	**n**	**Age**	**Design of brain imaging acquisition**	**Model**	**Timing (GD)**	**Neuroimaging type**	**Key MRI findings**
11	Ooi Y, et al. (2018), *Magnetic Resonance in Medical Science*	Rats, Wistar, M	14 (PND 35) & 10 (PND 70)	PND 35 and 70	CS	IP LPS; 100 µg/kg	16	T2-weighted sMRI (*in vivo*) (11.7T); resolution=78 x78x250µm^3	● Number of dilated VRSs significantly increased in LPS-offspring at PND35 but not PND70
12	Sharabi H, et al.(2018), *Neuroscience Research Article (IBRO)*	Rats, Sprague-Dawley, M	6/condition (LPS-NAC; LPS-SAL; SAL-SAL; 18 litters)	PND 25	CS	IP LPS; 500 µg/kg	18	DTI (*in vivo*) (9.4T); resolution=156x156x800µm^3	● MD: LPS-SAL > SAL: pontine-tract/spinal-tract, medial lemniscus/external capsule, entorhinal ctx, corpus callosum/external capsule, geniculate body, auditory ctx, mammillary body, posterior thalamic nucleus, sub thalamic nucleus, sensory ctx, thalamus ventroposterior-medial, amygdala, hypothalamus, thalamus, fimbria, CA1 and CA3 ● MD: LPS-NAC = SAL: callossum/external capsule, auditory ctx, mammillary body ● RD: LPS-NAC < LPS-SAL = CTL: medial lemniscus, entorhinal ctx, inferior superior colliculi, corpus callosum/external capsule, deep mesencephalic nucleus, audtory ctx, mammillary body, posterior thalamic nucleus,

									hypothalamus, thalamus, fimbria, CA1 and CA3
13	Zhang Z et al. (2018), *Neurobiology of Disease*	Rabbits, New Zealand White, NS	2-3/group (LPS & SAL) (5 litters);	PND 1, 5, 7-9	LG	IU LPS; 20 µg/kg	28	PET: [11C]-(R)-PK1195 tracer (TSPO) & T2-weighted sMRI (*in vivo*) (4.7T and microPET R4 tomograph); resolution=NA	● Increased TSPO binding in LPS exposed kits vs. SAL kits at all ages.
14	Crum WR et al. (2017), *Brain, Behaviour, and Immunity*	Rats, Sprague-Dawley, M	10 POL (8 dams) & 10 SAL (3 litters)	PND 50, 100, 180	LG	IV POL; 4 mg/kg	15	T2-weighted sMRI *(in vivo*) (7T); resolution=234x234x600µm^3	● POL had smaller ACC and HP volume. ● TBM: PND50-100: POL < SAL in prefrontal, motor, somatosensory, auditory and visual ctx, dorsal thalamic nuclei, ventral midbrain and brainstem; POL>SAL in ventricular, striatal, HP, ventral thalamic, and WM volumes. ● No differences TBV or STR.
15	da Silveira VT, et al. (2017), *International Journal of Developmental Neuroscience*	Mice, C57BL/6, M	12 POL (6 GD9 and 6 GD17; 8 litters); 12 SAL (6 GD9 and 6 GD17; 6 litters)	1 year of age	CS	IV POL; 5 mg/kg	9 or 17	T2-weighted sMRI (*in vivo*) (4.7T); resolution= NA (1mm thick slices)	● TBV reduced in both GD9 and GD17 POL groups ● No differences on normalized LV volume (to TBV)
16	Ginsberg Y et al. (2017), *Neuroscience*	Rats, Sprague-Dawley, F	6/condition (LPS-MG, LPS-SAL, SAL-MG, SAL-SAL; 18 litters)	PND 25	CS	IP LPS; 500 µg/kg	18	DTI & T2-mapping (*in vivo*) (7T); resolution=150x200x1000µm^3; 15 encoding directions	● ADC: LPS>SAL: entorhinal ctx, superior colliculus, cingulate ctx, corpus callosum, external capsule, auditory ctx, hypothalamus, thalamus, CA1 of HP ● T2 levels: LPS>SAL: periventricular fiber system (i.e. corpus callosum, sub thalamic radiation, external capsule, forceps major), ctx, thalamus ● MG pre-treatment resulted in T2 and ADC levels similar to CTLs
17	Richetto et al. (2016), *Cerebral Cortex*	Mice, C57BL6/N, M	8 POL(8 litters); 6 SAL	PND 84	CS	IV POL; 5 mg/kg	17	T2-weighted sMRI, mcDESPOT (includes T1 and T2 with	● POL > SAL: R primary motor ctx, somatosensory ctx, and visual ctx, crus1 ansiform lobule, simple lobule, and inferior cerebellar peduncles

			(6 litters)					B1 correctionand MWF (*ex vivo*; 7T); resolution for T2-weighted=112 .5μm^3, mcDESPOT= 150μm^3	• POL < SAL: bilaterally in piriform ctx, anterior commissure, interfasicular nucleus, third ventricle, L periaqueductal gray nucleus, L external capsule, L fimbria, R amygdala, R ventral mesencephalon, cerebellar lobule, paraflocculus and paramedian lobule of cerebellum • T1-mapping: POL>SAL: nucleus accumbens, inferior cerebellar peduncles • T2(spin-spin) relaxation: POL<SAL: piriform, PFC, ACC, insular, retrospelinal granular, motor, somatosensory, visual, and auditory cortices, hypothalamus, ventral thalamus, HP, ventral mesencephalon, cerebellum • MWF increased significantly in POL in ctx, HP, cerebellar gray and white matter
18	Li Q et al. (2015), *Translational Psychiatry*	Mice, C57BL6/N, M	21 POL (8 for n-3 and 7 for n-6; 3 litters), 17 SAL (6 n-3 and 11 for n-6; 3 litters)	PND84-89	CS	IV POL; 5 mg/kg	9	1H-MRS and T2-weighted sMRI (*in vivo*) (7T); resolution=109x109x480μm^3; 1H-MRS voxel size=1.2x2.6x2.5mm^3	• Increase in NAA/Cr and decrease in mIns/Cr in n6-POL group (vs. n6-SAL) • Both NAA/Cr and mIns/Cr values normalized in n3-POL groups (no difference with SAL)
19	Vernon AC, et al.(2015), *European Neuropsychopharmacology*	Rats, Sprague-Dawley, M	10 poly I:C (8 litters); 10 saline (3 litters)	PND50, 100, 180	LG	IV POL; 4 mg/kg	15	1H-MRS in PFC T2-weighted sMRI *(in vivo*; 7T); resolution=234x234x600um^3, 1H-MRS voxel size=3.8x2.2x2.0mm^3	• PND 50-100 POL>SAL: NAA+NAAG, Glu:tCR, GLX:tCr (not statistically significant after post-hoc correction), and decreased levels of Tau:tCr
20	Arsenault D et al. (2014), *Open Journal of Medical Psychology*	Mice, C57BL/6, both	39-40 LPS; 47-52 SAL (30 litters)	PND37-39 [18F]FPEB; PND42-44 [11C]PBR28	CS	IP LPS; 120 μg/kg (3 days)	15, 16, 17	PET: [18F]FPEB tracer (mGluR5) and [11C]PBR28 tracer (inflammation) (*in vivo*; NA); resolution=17	• LPS did not change [11C]PBR85 binding in any ROIs (inflammation) • [18F]FPEB binding (mGluR5) reduced in LPS offspring HP

								0x170x170µm^3	
21	Malkova NV, et al. (2014), *PNAS*	Mice, C57BL/6J, M	6 poly I:C (3 litters); 6 saline (3 litters)	PND 70-84	CS	IP POL; 5 mg/kg	10, 12, 14	"functional" MnCl2 enhanced RARE (*in vivo*; 11.7T); resolution=100µm^3	• POL: greater manganese (Mn2+) accumulation due to DOI in STR, somatosensory ctx, primary and secondary motor ctx, somatosensory (upper and lower limb), orbital ctx, infralimbic ctx, dorsal ACC, dorsal tenia tecta, medial dorsal thalamus • Parafascicular thalamic nucleus only activated by DOI in POL offspring
22	Bauman MD et al. (2013), *Translational Psychiatry*	Rhesus macaque, Both	4 IgG-ASD, 2 IgG-CON, 5 untreated	1, 3 and 6 months, 1 and 2 years	L	IV IgG antibody (15-20mg)[1]	30, 44, 58, 72, 86, 100	T1- weighted sMRI (*in vivo*; 1.5T); resolution=625x625x700µm^3	• IgG-ASD offspring had faster TBV growth than IgG-Controls for TBV (3 to 6 months) • Male IgG-ASD offspring had larger frontal, occipital, but not parietal or temporal lobes at 2 years • WM volume increase in frontal, occipital, and parietal lobes
23	Beloosesky R et al. (2013), *American Journal of Obstetrics and Gynecology*	Rats, Sprague-Dawley, F	5 LPS-NAC, 5 NAC-LPS-NAC, 8 SAL-LPS-SAL, 6 SAL-SAL-SAL; (1 females/litter/group)	PND 25	CS	IP LPS; 500 µg/kg	18	DTI & T2-weighted sMRI (*in vivo*; 7T); resolution for DTI=150x200x1000µm^3, 15 encoding directions, T2=75x150x1000µm^3	• T2 levels: LPS > controls: visual ctx, cingulate ctx, periaqueductal gray, dorsal hippocampal commissure, corpus callosum, external capsule, dentate gyrus, substantia nigra, geniculate body, HP, auditory ctx, piriform ctx, cingulum, thalamus, reticular thalamic nucleus, STR, insular ctx, and CA3 • T2 levels: LPS-NAC > LPS in visual ctx, cingulate ctx, periaqueductal gray, dorsal HP, corpus callosum, entorhinal ctx, dentate gyrus, substantia nigra, HP, auditory and piriform ctx, cingulum, thalamus, STR, insular ctx, CA3 • ADC: LPS >CTL: posterior thalamic nucleus, ventroposterior-medial nucleus of thalamus, hypothalamus, motor ctx (M1/M2) • ADC: LPS-NAC > LPS post. thalamic nucleus, hypothalamus, motor ctx; CTL similar to LPS-NAC
24	Bergeron et al. (2013), *Develop*	Rats, strain unclear, both	3 GBS; 13 control	PND150	CS	IP GBS serotype Ia; 1 × 109	19, 20, 21, 22	T2-weighted sMRI (*in vivo*; 7T); resolution=12	• GBS-exposed males (not females) had enlarged lateral ventricles

	mental Neurosc ience		s (26 litters)			CFU/100 µl		5x125x1000µ m^3	• Both sexes had reduced thickness of periventricular WM
25	Kannan S et al. (2011), *Develop mental Neurosc ience*	Rabbits, New Zealand White, NS	8 LPS (6 litters); 6 (5 litters) SAL; 4 (3 litters) no-surgery CTL,	PND 1	CS	IU LPS; 20 µg/kg	28	PET: [11C]-(R)-PK1195 tracer (TSPO) & T2-weighted sMRI (*in vivo*; 4.7T and microPET R4 tomograph); resolution=N A	• Increased TSPO binding in the LPS exposed kits compared to control kits
26	Kannan et al. (2011), *Journal of Cerebra l Blood Flow and Metabol ism*	Rabbits, New Zealand White, NS	5 (5 litters) LPS, 5 (4 litters) SAL, 4 kits (3 litters) non-surgica l CTL	PND 1	CS	IU LPS; 20 µg/kg	28	PET:[11C]-a[11C]methyl-L-tryptophan (AMT; tryptophan metabolism) tracer & T2-weighted sMRI (*in vivo*; 4.7T and microPET R4 tomograph); resolution=15 6x156x800µ m^3	• Decreased binding in LPS group compared to both control groups • SAL group was lower than no intervention controls
27	Piontke witz Y et al. (2011), *Biologic al Psychiat ry*	Rats, Wistar, both	158 POL (32 litters); 164 SAL (28 litters)	PND 35, 46, 56, 70, 90	LG + CS	IV POL; 5 mg/kg	15	T2-weighted sMRI (*in vivo*; 7T); resolution=11 7x117x1000µ m^3	• Smaller HP volume in POL over time (except at PND 35) • LV volume significantly larger in male POL group starting at PND 56 • PFC volume decline began on PND 56 in POL males, PND70 in SAL males and POL females, and was absent in SAL females • STR volume smaller in POL offspring • No TBV differences
28	Willette AA et al. (2011), *Behavio ural Brain Researc h*	Rhesus macaque, both	9 (1 at 2ng/kg, 8 at 4ng/kg) LPS; 9 CTL (2 IV SAL injectio n and 7 not handle d)	1 year	CS	IV LPS; 2 or 4 ng/kg	125 and 126	T1- and T2-weighted sMRI (*in vivo*; 3T); resolution=23 4x234x498µ m^3	• TBV of LPS monkeys was slightly larger (5.9%) • Mean global WM significantly increased (8.8%) • Marginally thicker GM in R parietal and frontal lobes • Thinner GM in medial temporal lobe
29	Girard S et al. (2010), *The Journal*	Rats, Lewis, NS	6 LPS; 6 SAL (image d dams)	GD17 (pre-LPS) and GD20	LG	IP LPS; 200 µg/kg	18, 19, 20 every 12	T1- and T2-weighted sMRI (*in vivo*; 7T); resolution=23	• Decreased T2-weighted signal intensity and clearance rate (10%) in placentas (GD20) LPS-exposed dams

	of Immunology			(post-LPS) for placenta			hours; 6 total)	4x234x1500µm	
30	Li Q et al. (2010), *Neuroimage*	Mice, C57BL6/N, M	14 POL (GD9=8, GD17=6); 8 (GD9=3, GD17=5) SAL	PND 84	CS	IV POL; 5 mg/kg	9 or 17	DTI (*ex vivo*; 7T); resolution=125x125x350µm^3, 30 encoding directions	● GD9 and GD17 POL: lower FA in the L amygdala and cerebral peduncles and R fimbria, and higher FA in L stria medullaris ● GD9 POL: lower FA in ACC, ventral STR, external capsule, and higher FA in L fimbria, lateral septal area, and PFC ● GD17 POL: lower FA in the R ventral subicular regions and increased FA in R stria medullaris and amygdala/piriform ctx
31	Short JS, et al. (2010), *Biological Psychiatry*	Rhesus macaque, both	12 H3N2; 7 CTL	1 year	CS	IN H3N2[3]	119	T1- and T2-weighted sMRI (*in vivo*; 3T); resolution=273x273x500µm^3	H3N2 exposure: ● Decreased TBV and cortical GM, cerebellar WM, trend decrease in TBV and WM increases in LV ● Decrease in cingulate and parietal ctx GM ● Decreased WM volume in L parietal region ● Greater WM volume in cingulate ctx ● Decreased bilateral amygdala volume (uncorrected) ● No differences in HP or STR
32	Fatemi SH, et al. (2009), *Schizophrenia Research*	Mice, C57BL/6, M	4 H1N1 (4 litters); 3 CTL (3 litters) (per age)	PND 0, 14, 35, 56	CS	IN H1N1[2]	16	DTI & T2-weighted sMRI (*ex vivo*; 11.8T); resolution for PND0=70x70x74µm^3, PND14-56=117x117x78µm^3; 6 encoding directions	● Decreased cerebellar volume (PND 14) and ventricular volume (PND 0) ● Decreased FA in R internal capsule (PND 0) ● Increased FA in corpus callosum (PND 14) and R middle cerebellar peduncle (PND 56)
33	Fatemi SH et al. (2009), *European Neuropsychopharmacology*	Mice, C57BL/6, M	4 H1N1 (4 litters), 3 CTL (3 litters) (per age)	PND 0, 14, 35, 56	CS	IN H1N1[2]	16	DTI & T2-weighted sMRI (*ex vivo*; 11.8T); resolution for PND0=70x70x74µm^3, PND14-56=117x117x78µm^3; 6 encoding directions	● Decreased TBV (7%; PND 14) and HP volume (6%; PND 35). ● No differences in FA in HP white matter (trending increase at PND 14)
34	Li Q et al. (2009),	Mice, C57BL6/N, M	14 POL (GD9=	PND 84	CS	IV POL; 5 mg/kg	9 or 17	T2-weighted sMRI (*in vivo*; 7T);	● No differences in TBV and WMV for GD9 or GD17 POL ● GD9 POL: larger LV volume

	PLoSOne		8, GD17=6), n=8 SAL (3GD9, 5 GD17)					resolution=97x97x250µm^3	• GD17 POL: larger 4th ventricle
35	Piontkewitz Y et al. (2009), *Schizophrenia Bulletin*	Rats, Wistar, M	16 POL (8-16 litters), 12 SAL (6-12) (1-2 rats per litter)	PND35 and 120	LG	IV POL; 5 mg/kg	15	T2-weighted sMRI (*in vivo*; 7T); resolution=117x234x1500µm^3	• No HP or LV volume differences at PND 35 • Decreased HP and increased LV at PND 120 • RIS treatment (high and low) prevented volume alterations in POL groups • High risperidone had decreased TBV compared to CTL
36	Piontkewitz Y et al. (2009), Biological Psychiatry	Rats, Wistar, M	81 POL (28 litters), 72 SAL (26 litters)	PND35 and 120	LG	IV POL; 5 mg/kg	15	T2-weighted sMRI (*in vivo*; 7T); resolution=117x234x1500µm^3	• No volume differences at PND 35 • Decreased HP and increased LV volume in at PND 120 • No differences at PND 120 following adolescent CLZ pre-treatment
37	Saadani-Makki F, et al. (2009), *Journal of Child Neurology*	Rabbits, New Zealand White, NS	5 LPS (3 litters), 5 SAL (4 litters)	PND 1	CS	IU LPS; 20 µg/kg	28	DTI & T2-weighted sMRI (*ex vivo*; 4.7T); resolution=250x250x700µm^3, 6 encoding directions	• Decrease in e1 &in FA in LPS group in periventricular WM
38	Fatemi SH et al. (2008), *Schizophrenia Research*	Mice, C57BL/6, M	4 H1N1 (4 litters), 3 CTL (3 litters) (per age)	PND 0, 14, 35, 56	CS	IN H1N1[2],	19	DTI & T2-weighted sMRI (*ex vivo*; 11.8T); resolution for PND0=70x70x74µm^3, PND14-56=117x117x78µm^3; 6 encoding directions	• Decreased TBV (4%) at PND 35 • Decreased FA in the corpus callosum at PND 35
39	Kannan S et al. (2007), *Journal of Nuclear Medicine*	Rabbits, New Zealand White, NS	4 (3 litters) 30ug/kg, 4 (4 litters) 20 ug/kg LPS; 4 (3 litters) SAL	PND 1	CS	IU LPS; 20, 30, 0r 40 µg/kg	28	PET: [11C]-(R)-PK1195 tracer (TSPO) & T2-weighted sMRI (*in vivo*; 4.7T and microPET R4 tomograph); resolution=156x156x500µm^3	• Increase TSPO binding in the LPS exposed (20 and 30ug/kg) kits (greater increase for 30ug/kg) relative to controls kits

ACC: anterior cingulate cortex, ADC: apparent diffusion coefficient, AMT: α[11C]methyl--tryptophan, CA: cornu Ammonis, CS: cross sectional, CTL: control, ctx: cortex, DOI: 2,5-Dimethoxy-4-iodoamphetamine, DTI: diffusion tensor imaging, DWI: diffusion weighted imaging, F: female, GBS: group B streptococcus, GD: gestational day, GM: gray matter, ^{1}H-MRS: proton magnetic resonance spectroscopy, HP: hippocampus, IP: intraperitoneal, IU: intrauterine, IV: intravenous, L: left, LG: longitudinal, LPS: lipopolysaccharide, LV: lateral ventricle, M: male, mcDESPOT: multicomponent-driven equilibrium single pulse observation of $T_1$and T_2, MD: medial diffusivity, MG: magnesium sulfate, NAC: N-acetyl aspartate, NS: not specified, PET: positron emission tomography, PFC: prefrontal cortex, POL: polyinosinic:polycytidylic acid, R: right, RD: radial diffusivity, rs-fMRI - resting state functional magnetic resonance imaging, SAL: saline, sMRI- structural magnetic resonance imaging, STR: striatum, T - Tesla, TBV: total brain volume, TSPO: Translocator protein, VRS: Vichrow-Robin spaces, WM: white matter

[1] IgG antibody isolated from women whose children had ASD Women also tested positive for maternal autoantibody reactivity to fetal brain proteins at 73 kiloDalton

[2] Dilution of $10^{-4.5}$ of 6.5 log 10 (CCID50) per 0.1ml human influenza virus in 90ul of minimum essential medium

[3] 10^{7} EID50 of virus via 1-mL infusion

* Study number aligns with **Figure 1**

3.1. Human studies

As summarized in **Figure 1**, 3 studies performed neuroimaging (structural MRI [sMRI] and diffusion weighted imaging [DWI]) on human fetuses in the 1st, 2nd, and 3rd trimesters of mothers who had cytomegalovirus (Birnbaum et al. 2017) (dark green) and in the 3rd trimester of mothers who had *Toxoplasma gondii* infection (dark blue) (Diebler, Dusser, and Dulac 1985; Dhombres et al. 2017). Five studies performed neuroimaging within the first year of life, one study imaged (sMRI & DWI) neonates at 5 days old (sMRI & DWI) exposed to chorioamnionitis (Jenster et al. 2018) (light orange). Three studies imaged offspring within the first 2 months of life. In 2 of these, neuroimaging (sMRI or resting state functional MRI [rs-fMRI]) was performed in 4 week old neonates for whom maternal IL-6 measures were taken (Graham et al. 2018; Rudolph et al. 2018) (pink). One study imaged (computed tomography [CT]) offspring exposed to *toxoplasma gondii* between 0-2 months of life (Diebler, Dusser, and Dulac 1985). These offspring were imaged again at 34-42 weeks, and 1-2 years of age. Two other studies also investigated offspring within the first year of life (34-42 weeks), 2 of which had measures of maternal IL-6 and CRP (rs-fMRI or sMRI or diffusion tensor imaging [DTI]) (Spann et al. 2018; Rasmussen et al. 2018). Finally, one study (sMRI) was performed in adults with schizophrenia (mean age of 40) for whom maternal IL-8 measures were recorded (Ellman et al. 2010).

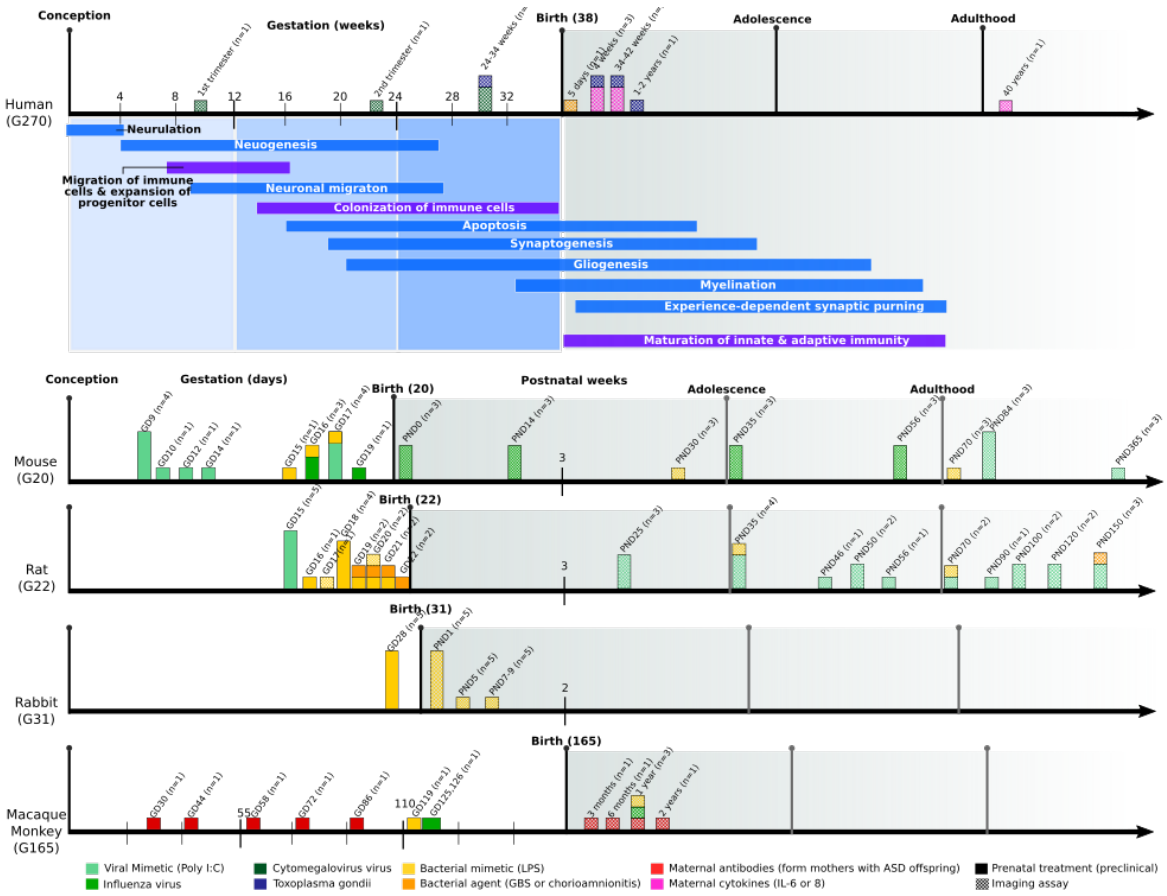

Figure 1. Summary of MRI-based MIA-exposure findings across 5 species. The steps of brain (blue bars) and immune system (purple bars) development are highly organized from gestation to early postnatal life; however, the timing of these neurodevelopmental processes differs between species. The short- and long-term effects of maternal immune activation depend on many factors, including the time window of development in which they are experienced, thus understanding homologies and differences between human and animal model development is critical. This figure summarizes the 39 reviewed studies in terms of the gestational timing of MIA and the timing at which neuroimaging was performed in the offspring. Studies are numbered 1-39 (see tables 3.1 and 3.2); this number is used as reference in the figure. Different pathogens or immune activators are color coded as follows: viral infections are green, with light green for viral mimetics (poly I:C), green for influenza virus, dark green for cytomegalovirus. Bacterial infections are in yellow for the mimetic LPS, and orange for group B streptococcus (GBS) and chorioamnionitis. Maternal antibodies are in red and maternal cytokines are in pink. Solid bars represent prenatal treatment and are relevant for the preclinical studies, whereas the hatched bars refer to timing of neuroimaging of the offspring (pre- or postnatally).

3.2. Animal studies

As outlined in **Figure 1** and **Table 2**, 10 studies modelled MIA in mice, 4 of which induced MIA at gestational day (GD) 9 using poly I:C (green) and imaged offspring (sMRI, DTI, or proton magnetic resonance spectroscopy [^{1}H-MRS]) in adulthood (3 studies on postnatal day (PND) 84 and 1 at PND 365) (Qi Li et al. 2009, 2010; Q. Li et al. 2015; da Silveira et al. 2017). One study induced MIA with poly I:C at GD10, 12, and 14, and also imaged offspring in adulthood (PND 70-84) using manganese chloride enhanced MRI (MEMRI) (Malkova et al. 2014). One study induced MIA using LPS (yellow) at GD 15, 16, and 17, and assessed neuroinflammation (PND 37-39) and glutamate receptor function (PND 42-44) in adolescence using PET imaging (Arsenault et al. 2014). MIA was induced at GD 16 in 2 studies, and GD 19 in 1 study using H1N1 influenza (light green), and offspring were imaged using DTI or sMRI *ex vivo* at PNDs 0, 14, 35, 56 (Fatemi et al. 2008; Fatemi, Folsom, Reutiman, Abu-Odeh, et al. 2009; Fatemi, Folsom, Reutiman, Huang, et al. 2009). Finally, 4 studies investigated the effects of poly I:C injection at GD 17 on adult offspring (PND 84 using sMRI, DTI, or ^{1}H-MRS) (Qi Li et al. 2009, 2010; Richetto et al. 2017; da Silveira et al. 2017).

Ten rat studies are reviewed, as shown in **Figure 3.1**. Five studies investigated the effects of MIA at GD 15 using poly I:C in adolescent and adult offspring; one study performed sMRI at PNDs 35, 46, 56, 70, 90 (Piontkewitz, Arad, and Weiner 2011b), 2 did sMRI at PND 35, 120 (Piontkewitz, Arad, and Weiner 2011a; Piontkewitz, Assaf, and Weiner 2009), and 2 did sMRI and ^{1}H-MRS at PNDs 50, 100, 180 (Vernon et al. 2015; Crum et al. 2017). Many studies used LPS to induce MIA: 1 at GD16 with sMRI in offspring at PND 35 and 70 (Ooi et al. 2017), 3 at GD18 with offspring imaged (sMRI & DTI) at PND25 (Beloosesky et al. 2013; Ginsberg et al. 2017; Sharabi et al. 2018), and 1 investigated effects repeated LPS administration (GD 18, 19, 20) on placentas *in utero* (GD 17 and 20) (Girard et al. 2010). Finally, one study investigated MIA (induced by Group B streptococcus [GBS] serotype) late in gestation (GD 19, 20, 21, and 22), and imaged (sMRI) offspring in adulthood (PND 150) (Bergeron et al. 2013).

In New Zealand White Rabbits, 5 studies investigated the effects of MIA late in gestation (GD28 of 31) on offspring at PND 1, 5, and 7-9; 4 studies used PET imaging (3 measured inflammation with a radioligand for Translocator protein (TSPO) (Kannan et al. 2007; Z. Zhang et al. 2018; Kannan, Saadani-Makki, Balakrishnan, Chakraborty, et al. 2011), 1 measured tryptophan metabolism with α[11C]methyl--tryptophan (AMT) tracer) (Kannan, Saadani-Makki,

Balakrishnan, Dai, et al. 2011), and 1 used DTI (Saadani-Makki et al. 2009). Finally, in the rhesus monkey, 1 study investigated the effects of MIA exposure using human IgG antibodies isolated from mothers with ASD offspring (red) in the first 2 trimesters (GD 30, 44, 58, 72, 86, 100), and imaged (sMRI) offspring at 1, 3, and 6 months, and 1 and 2 years of age (Bauman et al. 2013). Two other studies investigated MIA at week 17 (GD 119 with H3N2 and GD 126 & 126 with LPS) and imaged offspring at 1 year of age (Short et al. 2010; Willette et al. 2011).

4. Discussion

4.1. Summary of key findings in humans

Studying MIA in humans is challenging; epidemiologic studies have limitations in defining individual exposures, whereas birth cohort studies may lack serial serologic measurements to verify recent infections, and thus few studies exist (Minakova and Warner 2018; Brown and Meyer 2018). Recent advances in neuroimaging allow for detailed investigation of structure and function in the developing brain. Using these methods, recent studies have demonstrated that exposure to *Toxoplasma gondii* in the first 2 trimesters leads to abnormal thickness of the germinal matrix (a highly vascularized region where neuronal and glial cells migrate from during 8-28 weeks gestation (Gleason and Back 2005)); it is also associated with severe neurological signs, including microcephaly, hydrocephalus, mental retardation, and blindness, and can result in a termination of pregnancy (McAuley 2014). Late infection (>30 weeks) is associated with less severe outcomes, but periventricular and intracerebral calcifications are still observed (Dhombres et al. 2017; Diebler, Dusser, and Dulac 1985). Infections with cytomegalovirus demonstrate some homologies as they also lead to hyperintensities in the periventricular WM, temporal, frontal, and parietal lobes, and caudate nucleus (Birnbaum et al. 2017; Lipitz et al. 2010). However, the association between gestational timing of cytomegalovirus infection and fetal outcomes is less clear. Further work is required to better understand if the gestational timing of infection and severity of neuroanatomical alterations is similar to toxoplasmosis. Similar to the other infections, chorioamnionitis was also found to damage periventricular WM and alter basal ganglia and thalamus development (Birnbaum et al. 2017).

Elegant work from the groups of Buss, Fair, and Spann has shown that maternal inflammation (serum IL-6 levels in all trimesters) is associated with subtle alterations in offspring. Fronto-limbic circuitry of the neonate (4 week old) brain was found to be altered, with observations of larger right amygdala volume, and greater bilateral amygdala connectivity to regions involved in sensory processing and integration (fusiform, somatosensory cortex, thalamus), learning and memory (caudate and parahippocampal gyrus), and salience detection (insula) (Graham et al. 2018); decreased fractional anisotropy (FA) of the uncinate fasciculus, a key frontolimbic WM bundle, was also observed (Rudolph et al. 2018). Additionally, maternal IL-6 concentration was predictive of neonatal functional brain connectivity in networks important for social, emotional, and cognitive development, and known to be impaired in neuropsychiatric disorders, such as the dorsal attention, salience, and subcortical networks (Woodward and Cascio 2015; Rudolph et al. 2018). Third trimester MIA (IL-6 and CRP) was also associated with strength of salience network connectivity in the mPFC, temporoparietal junction, and basal ganglia (Spann et al. 2018).

Only one retrospective study investigated the relationship between maternal pro-inflammatory cytokine (IL-8) levels during pregnancy and brain morphology of adults with schizophrenia spectrum disorders. They report higher IL-8 levels *in utero* to be associated with increased ventricular volume and decreased entorhinal and posterior cingulate volume (Ellman et al. 2010). Thus, MIA-exposure plays a key role in either inducing or exacerbating morphological alterations.

4.2. Summary of structural changes following prenatal MIA in preclinical studies

Preclinical studies investigate the effects of prenatal MIA at different gestational windows on offspring development from birth to adulthood. This provides us with a greater understanding of the long-term changes due to MIA. The majority of preclinical studies in the literature, and those included in this review, model MIA in mice and rats (69%). These adequately capture many features of embryogenesis and fetal brain development, such as neurulation, neurogenesis, neuronal differentiation and migration, and migration and colonization of immune cells (**Figure 3.1**). However, synaptogenesis, gliogenesis, and myelination begin postnatally in rodents, but prenatally (third trimester) in humans (Shoykhet and Clark 2011; Lebel and Deoni 2018), thus investigating the effects of MIA on these processes may be better modeled in other species such

as nonhuman primates, whose neurodevelopment is similar to the human (Gumusoglu and Stevens 2019). The discussion of preclinical findings has been divided below by gestational timing of MIA.

4.2.1. Early Gestation (rodents <GD10, rhesus monkey < ~GD82)

The time window we refer to as early gestation in rodents corresponds to the end of the first trimester in primate gestation. During this time, the developing brain is undergoing critical neurodevelopmental processes such as the initiation of neuronal and immune cell migration, neurogenesis, cortical plate formation, and microglial colonization (Selemon and Zecevic 2015; Semple et al. 2013; Clancy, Darlington, and Finlay 2001). Five studies investigated the effects of MIA in early gestation on offspring neonatal (1 rhesus monkey study) and adult (4 mouse studies) development. Rhesus monkeys exposed to maternal immunoglobulin G isolated from mothers whose offspring had ASD in the first 2 trimesters were found to have accelerated growth in total brain volume (TBV) between 3 and 6 months of life, and increased frontal and occipital lobe volume, driven by WM volume expansion at 1 and 2 years of life (Bauman et al. 2013).

Adult mouse offspring prenatally exposed to poly I:C early in gestation (GD 9) were found to have larger lateral ventricle volume (PND 84) (Qi Li et al. 2009), lower fractional anisotropy (FA) in the anterior cingulate, ventral striatum, external capsule, and amygdala (amongst other regions), and higher FA in the PFC, stria medullaris, fimbria, and lateral septum (Qi Li et al. 2010); increased N-acetylaspartate (NAA) and decreased myo-inositol (mIns) were observed in the PFC, indicative of neuronal and astrocytic dysfunction, respectively (Q. Li et al. 2015). Finally, only 1 study reported TBV reductions in very old mice (PND 365) following GD 9 MIA (poly I:C) (da Silveira et al. 2017). Effects on the adolescent brain remain to be elucidated.

4.2.2. Mid Gestation in Rodents (GD10-14)

Rodent mid-gestation corresponds to the early-middle second trimester in primate gestation; during this time, the blood-brain barrier is forming, immune cell and neuronal migration is ongoing as is neurogenesis in many midbrain and subcortical regions, and sex determination occurs (Matcovitch-Natan et al. 2016; Eggers and Sinclair 2012; Clancy, Darlington, and Finlay 2001; Semple et al. 2013; Selemon and Zecevic 2015). Several studies have investigated the effects

of prenatal poly I:C challenge during mid-gestation (GD 15) in rats. Adolescent male rats were found to have no volume alterations in regions of interest such as the hippocampus, lateral ventricles, and TBV; however, smaller striatal volume was observed in both male and female rats (Piontkewitz, Assaf, and Weiner 2009; Piontkewitz, Arad, and Weiner 2011a, [b] 2011).

Many alterations become apparent in both early and late adulthood, including decreased anterior cingulate (ACC) cortex, dorsal thalamic nuclei (Crum et al. 2017), hippocampal, striatal, and PFC volume (with 1 report of earlier decline in males) (Piontkewitz, Assaf, and Weiner 2009; Piontkewitz, Arad, and Weiner 2011a, [b] 2011). Similar regions (ACC, infralimbic area, caudate, dorsomedial thalamus) were also found to be more activated (using MEMRI) in adult poly I:C exposed offspring in response the hallucinogen 2,5-Dimethoxy-4-iodoamphetamine (Malkova et al. 2014). Interestingly, the parafascicular thalamic nuclei, which play a role in the pathogenesis of hallucinations, were only activated in MIA offspring (Malkova et al. 2014). Finally, aberrant neuronal function and glutamate signaling were also observed in the PFC (elevations in total NAA, glutamate, and glutamate+glutamine, and reductions in Tau (Vernon et al. 2015)). In summary, infection in mid-gestation leads to structural, functional, and neurochemical alterations to the PFC, amongst other key regions, which appear in adulthood, and may present earlier in males, in line with schizophrenia symptomatology (Meyer, Feldon, and Dammann 2011; Liemburg et al. 2016). However the neonatal and pre-adolescent period requires further investigation.

4.2.3. Late Gestation (GD15-21 mouse/rat; GD 28 rabbit)

Late gestation in rodents corresponds roughly to the end of the second trimester in primate development, where corticogenesis and cortical layer organization, synapto- and gliogenesis, and apoptosis are beginning; furthermore, neurogenesis of the hippocampus and crtical layers is peaking (Estes and McAllister 2016a; Knuesel et al. 2014; Clancy, Darlington, and Finlay 2001). The effects of MIA in late gestation have been investigated at the level of the placenta, which plays an important role in modulating the effects of inflammation on the fetus (Hsiao and Patterson 2012; Goeden et al. 2016). One study found that LPS exposure (GD 18-20) decreased T2-signal intensity and clearance rate (~10%) in the placentas (GD 20), indicative of placental damage and inflammation similar to chorioamnionitis (Girard et al. 2010).

A large number of studies investigated the effects of intrauterine LPS administration in late

gestation on the neonatal New Zealand white rabbit brain using PET and DTI. Interestingly, increased neuroinflammation, assessed using the TSPO tracer, is observed in a dose-dependent manner as early as PND 1 and can persist up to PND 17 (Z. Zhang et al. 2018; Kannan et al. 2007; Kannan, Saadani-Makki, Balakrishnan, Chakraborty, et al. 2011). Conversely, decreased cortical (i.e. frontal and parietal) serotonin was also observed at PND 1, as assessed by the AMT tracer (Kannan, Saadani-Makki, Balakrishnan, Dai, et al. 2011), as well as decreased FA in the periventricular WM (i.e. corpus callosum, anterior commissure, internal capsule, and corona radiata) (Saadani-Makki et al. 2009). Similarly, mouse offspring prenatally exposed to the human influenza strain H1N1 at GD 16 also had decreased FA in the right internal capsule at P 0, coupled with decreased ventricular volume.

Three studies investigated rats in peri-adolescence (PND 25) prenatally exposed to LPS at GD 18, and found widespread changes using both DWI and quantitative imaging. LPS exposure was again found to negatively impact periventricular WM, as well as the entorhinal, auditory, sensory cortices, hippocampus, caudate-putamen, hypothalamus, and thalamus (increased medial diffusivity (MD), apparent diffusion coefficient, and T2-signal intensity) (Sharabi et al. 2018; Ginsberg et al. 2017; Beloosesky et al. 2013). Similarly, mice who were prenatally exposed to H1N1 at GD 16 or GD 19 had decreased TBV and cerebellar volume, and increased corpus callosum volume, at PND 14 (Fatemi et al. 2008; Fatemi, Folsom, Reutiman, Abu-Odeh, et al. 2009; Fatemi, Folsom, Reutiman, Huang, et al. 2009).

Adolescent offspring prenatally exposed to LPS (GD 15, 16, 17) had reduced binding potential of the PET tracer [18F]FPEB, a radioligand for metabotropic glutamate receptor 5, in the hippocampus. Interestingly, no signs of neuroinflammation were found using [11C]PBR85, a radioligand for peripheral benzonitrile receptor 28 (Arsenault et al. 2014); neuroinflammation observed in the early postnatal period (Kannan et al. 2007; Z. Zhang et al. 2018) may normalize by adolescence, although different tracers were used. Adolescent rats were also found to have decreased hippocampal volume and a higher number of dilated Vichrow-Robin spaces, often associated with neurodevelopmental and neurodegenerative diseases, following MIA at GD 16 (H1N1, LPS respectively) (Fatemi, Folsom, Reutiman, Huang, et al. 2009; Ooi et al. 2017).

Three studies investigated the effects of prenatal poly I:C exposure at GD 17 in adulthood and found widespread alterations using sMRI and DTI. At PND 84, poly I:C exposed offspring had smaller anterior commissure, external capsule, and piriform cortex volumes (Richetto et al.

2017). Volume increases were observed largely in the cerebellum, a region sensitive to neurodevelopmental insult (Wang, Kloth, and Badura 2014), and the 4th ventricle (Richetto et al. 2017; Qi Li et al. 2009). Decreased T2-relaxation time was observed in similar regions such as the cerebellum, hippocampus, and piriform cortex, as well as many other cortical regions (PFC, ACC, insular, motor, somatosensory, visual, auditory cortices). WM tract integrity of the cerebral peduncle, fimbria, and subiculum was comprised following poly I:C exposure at GD 17 (decreased FA); some gray matter (GM) regions were also found to have decreased FA such as the amygdala and piriform area (Richetto et al. 2017; Qi Li et al. 2010). Finally, MIA induced by GBS exposure (GD 19, 20, 21, 22) decreased forebrain volume and increased lateral ventricle volume mainly in male offspring, with reduced periventricular external capsule thickness in older adult (PND150) rat offspring of both sexes (Bergeron et al. 2013). Thus, evidence suggests that MIA in late gestation may compromise placental function and lead to neuroanatomical and neurochemical alterations throughout the offspring lifespan.

4.2.4. Late Gestation exposure in primates (>GD110)

Synaptogenesis and myelination are actively occurring in the human third trimester, which corresponds to postnatal rodent development (Gumusoglu and Stevens 2019). Thus, the effects of MIA on these processes may be better studied in non-human primates given their similarly protracted intrauterine periods. Interestingly, 2 studies have investigated the effects of the bacterial mimetic LPS, and the influenza virus H2N3 on neonatal offspring development in the rhesus monkey. They found that offspring exposed to LPS at 17 weeks gestation had increased global WM volume, and thicker GM in the right parietal and frontal lobes, with thinner GM volume in the medial temporal lobe (Willette et al. 2011). Conversely, H2N3 exposure at 17 weeks of gestation resulted in increased LV volume, and a decrease in total and cortical GM volume and cerebellar WM. Decreased GM volume was observed in the cingulate and parietal cortex, whereas WM volume was also increased. Finally, decreased bilateral amygdala volume was also observed (Short et al. 2010).

4.3. Can structural brain abnormalities be prevented?

The current body of literature on prenatal MIA exposure provides compelling evidence for progressive neuroanatomical and behavioural alterations appearing throughout the lifespan, mimicking many neuropsychiatric disorders. A handful of preclinical studies included in this review have investigated various therapeutic manipulations administered either to the mother, or to the offspring, and found them to rescue some MIA-induced brain phenotypes (Sharabi et al. 2018; Piontkewitz, Assaf, and Weiner 2009; Piontkewitz, Arad, and Weiner 2011a; Ginsberg et al. 2017; Q. Li et al. 2015). Treatment with either antioxidants (e.g. N-acetyl cysteine) or anti-inflammatory compounds (e.g. IL-1Ra, magnesium sulfate) around the time of the maternal immune challenge were found to normalize offspring deficits, including alterations to WM/tissue integrity (MD or radial diffusivity [RD], or T2-signal) in young (PND 25) rats (Sharabi et al. 2018; Ginsberg et al. 2017). It is possible that these rescuing effects are a result of normalizing placental clearance ability and tissue integrity (T2 signal), as shown by Girard and colleagues (Girard et al. 2010).

Investigation of therapeutic interventions in the offspring has also been a point of interest, as they may be used during prodromal or high-risk phases to prevent the emergence of neuropsychiatric disorders. For example, treatment with atypical antipsychotic drugs, which have been shown to increase anti- and decrease pro-inflammatory cytokine production, in adolescent humans and in cell culture (Al-Amin, Nasir Uddin, and Mahmud Reza 2013; Kato et al. 2011) during an asymptomatic phase, successfully prevented lateral ventricle and hippocampal volume alterations in adult mice following prenatal poly I:C challenge (Piontkewitz, Assaf, and Weiner 2009; Piontkewitz, Arad, and Weiner 2011a). Similarly, administration of a diet rich in omega-3 polyunsaturated-fatty acids was shown to normalize MIA-induced NAA and mIns alterations (Q. Li et al. 2015). Several other therapies, such as probiotics (Hsiao et al. 2013), environmental enrichment (Connors et al. 2014), or maternal zinc (Chua et al. 2012; Coyle et al. 2009) have also shown promise in reducing schizophrenia or ASD behavioural or neurochemical aberrations.

4.4. Parallels between clinical and preclinical findings

Both clinical and preclinical studies included in this review suggest that prenatal exposure to maternal inflammation leads to widespread neuroanatomical alterations detectable throughout

the lifespan (fetus to adult). Periventricular WM is sensitive to damage following infection late in gestation in rabbit, rat, and mouse studies, and in human fetuses exposed to toxoplasmosis *in utero*. This gestational timing coincides with the beginning of WM development. Damage to this region may be a result of pro-inflammatory cytokines and diffuse activation of microglia within immature WM, leading to death or injury or pre-myelinating oligodendrocytes (Khwaja and Volpe 2008). Further, development of periventricular vasculature may also be impaired, resulting in further damage to this region (Dammann and O'Shea 2008). Periventricular WM is also in close proximity of ventricles and striatum where alterations are consistently observed in many clinical and preclinical studies.

Some human studies suggest that maternal infection early in gestation leads to more severe deficits in the offspring frontal, temporal, and parietal cortices and periventricular WM than exposure in late gestation. The preclinical findings do suggest that the timing of MIA may influence the severity or evolution of neuroanatomical changes; however, very few studies actually employed longitudinal designs to be able to adequately investigate this question. Even so, it appears that MIA in early gestation leads to accelerated brain growth early in life, and neurochemical alterations in the PFC (impaired neuronal and astrocytic function), as well as diffuse WM alterations in adulthood. Conversely, MIA in mid-gestation leads to changes that only appear in the adult brain, such as increased lateral ventricle, decreased hippocampus, and PFC volume, with more pronounced effects in males. Finally, MIA in late gestation seems to induce neuroinflammation and decreased cortical serotonin early in the lifespan, decrease glutamate receptor function in adolescence, followed by diffuse structural changes in adolescence and adulthood in the cortex and cerebellum.

There is also the possibility for a dose-dependent effect. In human studies in which mothers were infected with viral or bacterial pathogens, fetal and neonatal brain structure alterations were more severe than in studies investigating effects of IL-6 or CRP in healthy mothers on offspring. In the latter group, higher pro-inflammatory cytokine levels were associated with broader alterations to fronto-limbic and salience network connectivity. However, there is no long-term follow-up in these studies, making it difficult to determine how MIA affects developmental trajectories. Only 1 study investigated the relationship between maternal cytokine levels and brain anatomy in individuals with schizophrenia spectrum disorders and did indeed find associations between IL-8 and brain structure suggesting that *in utero* cytokine exposure does cause enduring

neuroanatomical changes. The clinical and preclinical studies included in this review provide strong evidence for the idea that exposure to maternal infection or inflammation *in utero* leads to neurodevelopmental changes. There is a wide body of literature confirming that behavioural, neurochemical, and cellular changes are also detectable, but this work is outside of the scope of this review (Gumusoglu and Stevens 2019; Meyer 2014; Knuesel et al. 2014; Estes and McAllister 2016a; Solek et al. 2018).

4.5. Parallels between MIA-induced brain alterations and those observed in patients with ASD and schizophrenia

MIA-exposure is associated with deficits in neuroanatomy and behaviour relevant to both schizophrenia and ASD pathophysiology. Notably, these disorders are both of prenatal origin and overlap to some extent in terms of symptomatology (e.g. difficulties with social interaction, emotion, verbal and nonverbal communication, and odd or inflexible behaviour (Stone and Iguchi 2011; Hommer and Swedo 2015; Gumusoglu and Stevens 2019; Park et al. 2018)). Further, there are similarities with respect to the brain regions affected in each illness.

Neuroanatomical alterations commonly observed in patients with schizophrenia include: widespread cortical thinning, most pronounced in the frontal and temporal lobes, decreased hippocampal, thalamic, amygdala, nucleus accumbens and total brain volume, increased pallidum and ventricular volume, and WM abnormalities in the corpus callosum and corona radiata (Kelly et al. 2018; T. G. M. van Erp et al. 2016; Theo G. M. van Erp et al. 2018). Furthermore, aberrant glutamatergic signaling has often been observed, most commonly in the unmedicated state, in brain regions such as the ACC/medial PFC, hippocampus, and basal ganglia (Hu et al. 2015; Plitman et al. 2014; Iwata et al. 2018). Interestingly, comparable deficits are observed in MIA offspring, including lateral ventricle enlargement, volume decreases and glutamate dysregulation in the PFC and hippocampus in adulthood, and alterations to the periventricular WM in many of the rodent studies reviewed here (Piontkewitz, Assaf, and Weiner 2009; Piontkewitz, Arad, and Weiner 2011a; Arsenault et al. 2014; Piontkewitz, Arad, and Weiner 2011b; Crum et al. 2017; Vernon et al. 2015; Bergeron et al. 2013; Malkova et al. 2014).

Individuals with ASD have abnormalities in similar regions but with different directionality; cortical overgrowth in frontal, temporal, cingulate, and parietal lobes is commonly

observed in the first 2 years of life, as well as enlarged amygdala and cerebellum volumes (Schumann et al. 2010; Amaral, Schumann, and Nordahl 2008). Cortical overgrowth in the first 2 years of the rhesus monkey lifespan was also observed following MIA (Bauman et al. 2013) and cerebellar abnormalities were observed in mouse models (Fatemi et al. 2008). Finally, enlarged amygdala volume, as well aberrant fronto-limbic pathways, were associated with increased pro-inflammatory cytokine exposure in human neonates (Graham et al. 2018; Rasmussen et al. 2018).

There are many additional parallels between schizophrenia, ASD, and MIA models at the cellular level, including deficits in Purkinje cells, impaired expression of parvalbumin and reelin, excessive microglial activation, and altered dendritic morphology and synaptic pruning mechanisms (Careaga, Murai, and Bauman 2017; Keshavan et al. 2014; Canetta et al. 2016; Gao and Penzes 2015). It is noteworthy that this section of the review focuses specifically on similarities between MIA-induced brain alterations, as per the results of the included studies, and well-accepted findings from ASD and schizophrenia literature. Notwithstanding, there are several dissimilarities between the neuroanatomical alterations rendered by MIA and the literature surrounding ASD and schizophrenia. These discrepancies could in part be accounted for by an accumulation of risk factors, of which MIA is only one; however, a detailed discussion of these dissimilarities is beyond the scope of the review.

4.6. Male bias in preclinical studies

The human studies reviewed here were fairly balanced in their inclusion of males and female offspring; however, none of the studies investigated sex as a variable of interest to determine whether exposure to maternal inflammation affected male and female offspring differently. Moreover, of the preclinical studies reviewed, 6 did not specify offspring sex, 16 only studied males, 2 only studied females, and only 4 studies included both sexes in equal numbers. Unfortunately, this is representative of the general lack of balanced groups in preclinical research. Of the 4 studies that did include males and females, interesting sex differences emerged longitudinally. Male MIA-exposed offspring developed neuroanatomical deficits either earlier than females, such as decreased PFC volume, or had deficits that females did not, such as lateral ventricle enlargement (Piontkewitz, Arad, and Weiner 2011b). The consideration of sex as a variable would seem self-evident given the strong sex bias in prevalence, symptom presentation,

and treatment response in many neurodevelopmental disorders, yet very few preclinical studies include both males and females, with even fewer explicitly investigating sex differences (Coiro and Pollak 2019; Prata et al. 2017). A recent policy by the National Institute of Health aims to address this concern by mandating the consideration of using female cells and animals in preclinical research; hopefully this will balance the sex bias present in the literature.

4.7. Limitations

With respect to the included studies, there are a few noteworthy limitations. First, MIA models have a wide range of protocols that vary based on gestational timing, mode of delivery, dose, and immunogen used. Further, some less obvious, yet important, sources of variability include animal strain and genetic background, animal vendor, breeding, housing, amongst others reviewed by Weber-Stabdlbauer and Meyer, and by Kentner and colleagues (Kentner et al. 2019; Weber-Stadlbauer and Meyer 2019). All of these factors may lead to different downstream effects; the immunogen used determines the nature of the immune response, whereas the timing of exposure may interfere with different neurodevelopmental processes, altering the nature and severity of outcomes (Estes and McAllister 2016a; Knuesel et al. 2014). Further, only a few studies confirmed MIA or sickness behaviours in mothers (da Silveira et al. 2017; Crum et al. 2017; Vernon et al. 2015; Bergeron et al. 2013; Girard et al. 2010; Willette et al. 2011; Short et al. 2010), which is challenging to do in smaller species (i.e. taking a blood sample or increased handling could affect pregnancies (Kentner et al. 2019). Some ways to use variability as an opportunity for research, as suggested by Weber-Stadlbauer and Meyer, include investigating different MIA immunogens in different species, investigating susceptible and resilient mothers or placental placement to try to understand within- and between-litter phenotypic variation, and understanding the influence of microbiota on outcomes of MIA models (Kentner et al. 2019). Notably, it is critical for researchers to report methodological details of their chosen model to enhance transparency and comparability of these models across laboratories and species (Weber-Stadlbauer and Meyer 2019; Kentner et al. 2019).

Although animal models can never recapitulate a full spectrum of human behaviour, and acknowledging the fact that there are pronounced differences between rodent and primate brain development, there are also considerable cross-species alignment in terms of key developmental

milestones, well captured by a translational modality such as whole-brain imaging. The advantages to using preclinical MIA models to study the effects of maternal cytokines on brain development are that the immune response induced by viral and bacterial mimetics allow for precise timing of immunogenic impact, providing a better understanding of the links between immune activation and embryonic brain development. Further, preclinical brain imaging lends itself well to dense sampling, often a challenge in humans, and allows for post-hoc behavioural and post-mortem evaluation of these findings. However, it is noteworthy that much of the human work on elevated cytokine (IL-6) concentrations during pregnancy by the groups of Buss, Fair, and Peterson reflect chronic systemic low grade inflammation within a normal range, potentially due to poor nutrition, obesity, chronic stress amongst other factors, rather than an acute increase in inflammation due to infection or trauma. This work suggests that even modest variations in cytokines affect neonatal brain function; that being said, it does not lend itself well to study sensitive time windows of exposure as is done in the preclinical literature. There are a considerable number of human studies investigating maternal infection; however, these do not correlate offspring outcomes with specific cytokine levels.

There is also great variation in the MR image quality and image analysis methods, particularly within the preclinical studies. Many of the studies use low resolution images, with particularly thick slices (as thick as 1500 μm^3 in some rodent studies (Piontkewitz, Arad, and Weiner 2011a; Piontkewitz, Assaf, and Weiner 2009; da Silveira et al. 2017)), which prevents careful delineation of many structures within the rodent brain (see **Table 3.2**). Additionally, many rely on coarse structural volume estimations, relying on manual segmentation of these low-resolution images. Many of these studies may thus have insufficient power to detect subtle volume changes, as outlined by the power analysis by Lerch and colleagues, either based on low resolution or images, or low samples size, or both; in order to detect a within-subject 3% volume change in the hippocampus, it is recommended to have 10 mice per group at 4 timepoints with a resolution of 125um (Lerch et al. 2012). Further, many DWI studies included in this review use low resolution images with very few encoding directions and small sample sizes; however, the majority of these studies are over a decade old, and were performed when DWI was emerging as a technique (Fatemi, Folsom, Reutiman, Huang, et al. 2009; Fatemi, Folsom, Reutiman, Abu-Odeh, et al. 2009; Fatemi et al. 2008; Saadani-Makki et al. 2009). More recent work has employed 3D whole-brain voxel-wise approaches to investigate higher resolution images. Finally, considerations regarding

sample preparation should be noted, as *ex vivo* MRI is sensitive to perfusion artifacts (Cahill et al. 2012). Even so, some of the findings discussed in this review require replication with higher resolution data from different modalities including structural and functional MRI, as well as DWI, and potentially more quantitative MRI sensitive to myelin such as magnetization transfer ratio imaging, in addition to larger samples.

Offspring deficits are often measured cross-sectionally at different timepoints, using different modalities, making it challenging to determine the neurodevelopmental origins of specific deficits related to MIA-exposure. Our synthesis of these 39 studies suggests that more work is needed to understand the long-term consequences of MIA-exposure on offspring brain development. More specifically, there are very few studies that take advantage of the non-invasive nature of brain imaging to examine offspring longitudinally. This is critical as the consensus within the human literature is that to fully understand neurodevelopmental abnormalities, understanding how risk factors may impact developmental trajectories is critical. Without these homologous trajectories, it will be increasingly difficult to build translational "bridges" between observations from preclinical and clinical studies. Furthermore, performing *in vivo* MRI *in utero* or *ex vivo* MRI of embryos in models of maternal inflammation would provide us with crucial information regarding the evolution of brain structural changes following insult (Pedroni et al. 2014; Turnbull and Mori 2007; J. Zhang, Wu, and Turnbull 2018; D. Wu and Zhang 2016).

This review should also be considered in light of its own limitations. It is possible that relevant articles may have been omitted from the search due to the selection of search terms. Furthermore, this review focused on studies performing neuroimaging; however, in many cases, this was not their only assay. Discussing neuroanatomical changes in light of behavioural and cellular alterations is critical to furthering our understanding of how MIA primes the brain to be more sensitive to neurodevelopmental insult. A further limitation is lack of examination of a common pathway (or pathways) that may emerge due to MIA-exposure. In addition, it would be extremely interesting to extend this work by conducting a meta-analysis on reported volumes of certain structures, such as the hippocampus or lateral ventricles. However, we would certainly need some element of neuroanatomical standardization across species and gestational periods, as well as standardization of inflammatory agent, dose, and gestational timing used, which currently does not exist. We feel that this review draws attention to these nuances in the literature, and in future work, a meta-analysis could add significant value to this literature.

4.8. Conclusions and future directions

Converging evidence from clinical and preclinical studies suggests that MIA is a disease primer for various neurodevelopmental disorders. Better characterizations of age-, region-, and gender-specific effects on neuroanatomical development are critical to furthering our understanding of this risk factor. Careful characterization of MIA using high-resolution, multi-model longitudinal neuroimaging studies may help to elucidate many of these questions and identify regions of heightened vulnerability in which therapeutic interventions may be targeted. It may be interesting to combine MIA models with other relevant risk factors, such as schizophrenia- or ASD-relevant genetic mutations, or other environmental risk factors such as adolescent stress or drug use. Further, better integration of behavioural findings with brain structural changes (macro- and micro-scopic) may further our understanding of brain-behaviour relationships, and how they might be disrupted by MIA. Finally, improving the reproducibility of the model, with precise reporting and transparency, is of the utmost importance for moving the field forward.

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