Maternal immune activation in rodent models: A systematic review of neurodevelopmental changes in gene expression and epigenetic modulation in the offspring brain

Rebecca M. Woods a,*, Jarred M. Lorusso a, Harry G. Potter a, Joanna C. Neill b, Jocelyn D. Glazier a, Reinmar Hager a

a Division of Evolution & Genomic Sciences, School of Biological Sciences, Manchester Academic Health Science Center, Faculty of Biology, Medicine & Health, University of Manchester, Manchester, M13 9PT, United Kingdom
b Division of Pharmacy & Optometry, School of Health Sciences, Manchester Academic Health Science Center, Faculty of Biology, Medicine & Health, University of Manchester, Manchester, M13 9PL, United Kingdom

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ABSTRACT

Maternal immune activation (mA) during pregnancy is hypothesised to disrupt offspring neurodevelopment and predispose offspring to neurodevelopmental disorders such as schizophrenia. Rodent models of mA have explored possible mechanisms underlying this paradigm and provide a vital tool for preclinical research. However, a comprehensive analysis of the molecular changes that occur in mA-models is lacking, hindering identification of robust clinical targets. This systematic review assesses mA-driven transcriptomic and epigenetic alterations in specific offspring brain regions. Across 118 studies, we focus on 88 candidate genes and show replicated changes in expression in critical functional areas, including elevated inflammatory markers, and reduced myelin and GABAergic signalling proteins. Further, disturbed epigenetic markers at nine of these genes support mA-driven epigenetic modulation of transcription. Overall, our results demonstrate that current outcome measures have direct relevance for the hypothesised pathology of schizophrenia and emphasise the importance of mA-models in contributing to the understanding of biological pathways impacted by mA and the discovery of new drug targets.

1. Introduction

Neurodevelopmental disorders (NDDs) constitute a group of disorders, including schizophrenia and autism spectrum disorder (ASD), characterised by distinct behavioural phenotypes and, for ASD a very early age of onset (Mullin et al., 2013; Thapar et al., 2017; Weinberger, 1987). While effective treatment strategies exist for amelioration of positive symptoms of schizophrenia, there are currently no treatments licensed for management of cognitive or negative symptoms in schizophrenia, which cause the most significant reduction in quality of life and associated economic cost (Kaneko, 2018). Thus, global research effort is focused on understanding underlying aetiology, thought to comprise both genetic and environmental risk factors (Dunaevsky and Bergdolt, 2019; Meyer, 2019; Thapar et al., 2017). Critically, these disorders are hypothesised to arise from perturbed neurodevelopment, resulting in abnormal brain function, including aberrant neurotransmission and connectivity (Mullin et al., 2013; Thapar et al., 2017). The human brain is an incredibly complex organ, comprised of billions of neurons and glial cells organised into intricate signalling networks. Importantly, neurodevelopment commences early post-conception and continues into early adulthood (Stiles and Jernigan, 2010; Tau and Peterson, 2010). This protracted period of development constitutes a large window of vulnerability during which normal developmental trajectories can be disturbed by environmental stressors (Giussani, 2011; Sarkar et al., 2019).

Epidemiological studies have shown an increased prevalence of NDDs following viral epidemics, such as influenza (Adams et al., 1993; Brown et al., 2004; Canetta et al., 2014; Mednick et al., 1988). Collectively, these studies support the hypothesis that maternal infection increases the risk of exposed offspring developing NDDs (Brown and Derkits, 2010; Labouesse et al., 2015b; Solek et al., 2019). Therefore, as an environmental stressor, maternal immune activation (mA) following

* Corresponding author.
E-mail address: rebecca.woods@manchester.ac.uk (R.M. Woods).

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relationship between maternal infection and offspring NDDs (Fatemi et al., 2019; Meyer, 2019; Smith et al., 2007), specifically through elevations (Choi et al., 2016; Conway and Brown, 2019; Dunaevsky and Bergdolt, 2019) and neurodevelopmental trajectories which impact fetal neurodevelopment. Our aim is to provide a consolidated systematic review evaluating published quantitative changes in gene/protein expression; 4) Fetal and/or postnatal inflammation during pregnancy, is of particular interest in NDD research (Meyer, 2010, 2012). Importantly, these behavioural phenotypes emerge independent of a direct infection of the fetus by these immunogens. Instead, pivotal work has established the hypothesis that it is maternal inflammatory responses which impact fetal neurodevelopmental trajectories (Choi et al., 2016; Conway and Brown, 2019; Dunaevsky and Bergdolt, 2019; Meyer, 2019; Smith et al., 2007), specifically through elevations in maternal cytokines IL-6, TNFα, IL-1β, and IL-17A, which may either cross the placenta or alter its function (e.g. through reduced transport of essential nutrients), thereby influencing the availability of biosynthetic precursors required for normal neurodevelopment. These changes in fetal neurodevelopment are thought to be mediated by transcriptomic and epigenomic alterations. In agreement with this, alongside behavioural deficits, studies have also evaluated accompanying molecular changes in offspring brain tissue, including gene expression, neurotransmitter and neuroanatomical alterations, and epigenetic patterns (Boksa, 2010; Conway and Brown, 2019; Dunaevsky and Bergdolt, 2019; Gumusoglu and Stevens, 2019; Meyer and Feldon, 2010; Solek et al., 2018).

Investigations into the molecular mechanisms of mIA are critical in developing our understanding of NDDs, and are of particular importance when considering such models as platforms for the development of much needed therapeutic interventions (Meyer and Feldon, 2012). However, it is currently difficult to compare data between different studies, owing in part to methodological variability and inconsistencies in reporting (Harvey and Boksa, 2012; Kentner et al., 2019). Studies are beginning to identify methodological factors which contribute to inconsistencies between study outcomes, including caging systems, rodent strains, immunogen type, dosage and timing. Moreover, recent studies using poly(IC) have shown inherent variability in elicited immune response dependent on molecular weight, supplier and endotoxin contamination (Careaga et al., 2018; Kowash et al., 2019; Mueller et al., 2019). However, many published reviews which focus predominantly on molecular changes fail to report methodological disparities that may contribute to differences in molecular outcomes between studies. For preclinical research to be meaningful and impactful, we should standardise practices and improve experimental systems, reproducibility and therefore translational value of outcome data (Collins and Tabak, 2014; Fanelli, 2018; Kilkenny et al., 2010). In a laudable attempt to achieve this, several publications have called for thorough model validation and reporting within the mIA field (Kentner et al., 2019; Roderrick and Kenter, 2019).

In view of the emphasis for reproducibility in animal models and the significant unmet clinical need of therapeutic interventions for NDDs, it is critical that preclinical research is conducted methodically and within clear mechanistic frameworks. Research should aim to replicate findings, and attempt to identify robust molecular mechanisms underpinning disease pathology. To progress this aspect, we have conducted a systematic review evaluating published quantitative changes in gene/protein expression and epigenetic markers alongside methodological factors, as recommended in the reporting guidelines for mIA models (Kentner et al., 2019). To our knowledge, a comprehensive systematic review analysing neurodevelopmental changes in molecular patterns, together with methodological factors, has not previously been conducted within the mIA paradigm. Our aim is to provide a consolidated resource of published molecular changes in offspring brains following acute mIA, and to identify both consistent patterns and novel areas for future research.

2. Methods

2.1. Review process

The PRISMA-P guidelines (Liberati et al., 2009; Moher et al., 2015) were followed, and the protocol registered with PROSPERO (CRD42020171849). Search strategies were developed based on iterations of ‘maternal immune activation’; ‘rodent’ and ‘gene expression’. Where possible, medical subject headings (MeSH) were used in each database but with search strategies kept as similar as possible between individual databases. Final search strategies were checked by a University of Manchester librarian. Database searches were performed via the Ovid platform in MEDLINE (Ovid MEDLINE(R), EMBASE and PsycINFO on 22nd October 2020 with no restrictions applied (Supplement 1). Duplicates were excluded and remaining titles and abstracts screened for inclusion/exclusion criteria, followed by full texts. Reference lists from included full texts were then screened using the same criteria. The primary reviewer (RMW) performed the initial screening, with a total of 20 % of both abstract and full text screening checked between secondary reviewers (JML and HGP) with no discrepancies identified.

2.2. Inclusion criteria

Inclusion criteria were: 1) Rodent studies not using genetically modified strains; 2) Modelling of acute mIA during pregnancy alongside a comparable control; 3) Primary outcome of gene and/or protein expression analysed by a quantitative method; 4) Fetal and/or postnatal offspring brain tissue analysed for gene/protein expression; 5) Articles in English; 6) Articles representing a primary research paper; 7) Full text available (conference abstracts excluded). No restrictions were placed on the publication date. Based on these inclusion criteria, studies where the immune induction occurred in the uterus, vagina, neonate or in the father were not included as they did not constitute a model of mIA for our purposes. Likewise, as the aim was to evaluate the effects of acute mIA, we excluded studies that induced immune activation at more than one time point (>1 exposure). In addition, studies using cell counting or single cell gene expression analyses were also excluded because the aim was to evaluate quantitative gene expression changes in offspring brain tissues.

2.3. Data extraction and bias assessment

Using our pre-defined criteria we extracted data for: 1) Study title, first author and year of publication; 2) Rodent species and strain, age and weight; 3) Method of mIA, including: immunogen properties, dose, route of administration, gestational timing of immune induction, and supplier; 4) Details of control group; 5) Validation of mIA, including direct measurement of immune activation (cytokine or other markers of inflammatory response), maternal sickness behaviour and effects on litters; 6) Offspring cull time points; 7) Offspring brain tissues analysed; 8) Numbers in experimental groups; 9) Methodology of quantitative gene expression; 10) Primary outcome: results of quantitative gene expression analysis. Full texts were interrogated for quantitative changes in gene expression in mIA-affected offspring relative to control group, or a statistically significant directional change of change, either of which must have been reported alongside results of a statistical significance test. 11) Secondary outcome: details of epigenetic methodology and results. Included studies that performed epigenetic analyses alongside gene/protein expression analysis, were also interrogated for a quantitative value of change in epigenetic markers in mIA-affected offspring relative to control group, or a statistically significant directionality of change, either of which must have been reported alongside...
results of a statistical significance test. Statistical significance was noted as indicated in each study, but the consensus was a P ≤ 0.05 to be considered statistically significant. Any expression or epigenetic changes not meeting these criteria were considered non-significant/unchanged. Complete data extraction is available in Supplement 2.

Following data extraction, we assessed papers for potential bias. As this was a review of animal models, we opted to assess bias using the SYRCLE risk of bias (RoB) tool (Hooijmans et al., 2014), designed to aid authors in the appraisal of bias when conducting reviews of animal studies. The tool contains ten pre-defined questions of methodological bias including: selection, performance, detection, attrition and reporting bias. We adapted the SYRCLE RoB tool into a table format (Supplement 3) and interrogated the included full texts for each of the ten bias questions and answered them as yes (Y), no (N), unclear (U) or not applicable (NA) based on the methodology described in each study. All full text data extraction and bias assessments were performed by the primary reviewer (RMW) and confirmed by secondary reviewers (JML and HGP).

2.4. Qualitative synthesis

Papers were grouped by rodent species and immunogen, creating a total of six model groups for analysis: Influenza in mice; LPS in mice, LPS in rats; poly(I:C) in mice; poly(I:C) in rats and recombinant IL-6 (rhIL-6) in mice. Within these groups, we first considered the methodologies, comparing route of administration, dosage, immunogen properties and timing of immune induction. Validation of mA between research studies, evidence for bias and additional categories within the Kentner et al. (2019) guidelines were also assessed. We evaluated candidate gene expression changes by focusing on genes analysed by more than one study included in the review (Supplement 4). For consistency, only rodent gene IDs are used in-text while both gene and protein ID are provided in all tables. These genes were evaluated using gene ontology (GO) analysis (http://geneontology.org/) with Homo sapiens set as the reference gene set and a Fisher’s test with Bonferroni correction for multiple testing used for statistical analysis. GO for biological processes, molecular function and cellular component were all used to functionally assess the candidate genes analysed by more than one study (Supplement 5). We used gene ontologies as a guide to group candidate genes and outcomes by function that were subsequently assessed across tissue, age and model type. For studies using global gene expression analysis techniques, we evaluated outcome measurements by model type and tissue analysed. GO for biological processes was also performed for all genes identified as differentially expressed by non-candidate approaches to compare these results with those generated from candidate genes (Supplement 6). Likewise, for studies which performed epigenetic analyses, we evaluated results, firstly by mechanism assessed and then by model type and tissue analysed. Across all areas, we focused on whether these outcome measurements (expression or epigenetic changes) were 1) replicated or divergent between studies and 2) where divergent results were identified in outcome measurements, whether this occurred between studies employing different methodologies. Finally, we considered if any of the highlighted candidate genes (Supplement 4) were also identified in studies which perfomed global gene expression and/or epigenetic pattern analysis.

3. Results

3.1. General findings

The finalised search strategies (Supplement 1) resulted in 564, 1236 and 185 studies from MEDLINE(R), EMBASE and PsychINFO, respectively, with a total of 1291 studies screened after duplicate removal. The pre-defined inclusion criteria following screening of titles and abstracts were met by 198 studies. Of these, 116 studies were included after full text screening, and two studies subsequently included following screening of full text reference lists. This resulted in a total of 118 studies included in the final review (Fig. 1). Eighty-two final texts were excluded, the majority of which were omitted for occurrence of secondary interventions (pre/post-natal), no quantitative method of gene expression analysis or chronic mA (>1 immune induction/exposure). When the included 118 studies were categorised into rodent species and immunogen, poly(I:C) was the most prevalent immunogen administered, with mice the most commonly used rodent species. In addition, while influenza, poly(I:C) and rIL-6 were the most commonly used immunogens in mice, LPS was predominantly used in rats.

3.2. Study bias

The final 118 studies were all assessed for bias using SYRCLe’s RoB tool questions (Supplement 3). This assessment revealed key areas of bias across the studies included in the review, particularly, lack of randomisation and/or experimental blinding during allocation to treatment group or detection of outcome measurement. However, a leading source of bias across the 118 included studies was the allocation of a single sex, predominantly male offspring, to molecular analysis (Fig. 2). Studies have demonstrated sex-specific effects of mA on offspring brain development and behavioural outcomes (Meyer, 2014) and hence sex-bias in outcome measurements has the potential to confound sex-specific effects and misrepresent gene expression data between studies.

3.3. Heterogeneity of study design and implications for outcome measurements

In view of recent reporting guidelines published by Kentner and colleagues and the ARRIVE reporting guidelines for animal studies (Kentner et al., 2019; Kilkenny et al., 2010), we extracted data on methodology reported in the included studies (Supplement 2). An evaluation of the various procedural areas encompassing immune induction, experimental animals and housing, outcome measurements and model validations demonstrated inherent heterogeneity in the methodologies between research studies and a lack of reporting of experimental methods. A summary of the methodological components considered across the 118 studies included in the review are given in Fig. 3.

We and others have shown that immunogen dosage and rodent strain directly impact on dam immune response and subsequent offspring outcomes (Meyer et al., 2005; Morais et al., 2018; Mueller et al., 2018; Murray et al., 2019; Schwartzer et al., 2013). In addition, immunogen properties have also been shown to influence outcomes in rodent models. Poly(I:C) molecular weight characteristics and supplier have been demonstrated to impact molecular and behavioural outcomes in mA-exposed offspring (Careaga et al., 2018; Kowash et al., 2019; Mueller et al., 2019). Meanwhile, a study has shown that different bacterial LPS serotypes can induce disparate downstream immune responses in rodents in a model of preterm labour (Migale et al., 2015). Recent publications have advocated that transparency of methodology and thorough model validation are important for defining relationships between mA and brain abnormalities in offspring (Kentner et al., 2019; Murray et al., 2019; Roderick and Kenter, 2019). Therefore, we considered whether the studies within the scope of the review provided evidence of mA validation based on three common areas: dam sickness behaviours (as an assessment of dam behaviours, temperature or weight change), litter changes (including miscarriage/reabsorptions/smaller pups or litters) and direct measurement of immune activation (including viral titres, cytokine measurements or other measurements of inflammation). This assessment showed that 55 of the included studies provided evidence of mA validation and, of those that did, most used a direct analysis of maternal cytokines, specifically IL-1β, IL-6, IL-10, TNFα, IL-17A and IFNγ. Finally, it is also widely accepted that prenatal timing of immunogen exposure can influence distinct aspects of
neurodevelopment and thereby promote differences in offspring brain and behavioural phenotypes (Estes and McAllister, 2016; Meyer et al., 2006; Meyer, 2014). Further, when attempting to translate such disease phenotypes to humans, the gestational timing of immune induction is also confounded by the differences in gestational length between species (Clancy et al., 2001, 2007). The selected gestational timing of inducing mIA between studies and models included in the review, alongside a neurodevelopmental timeline, is shown in Fig. 4. Notably, while selection of treatment gestational days (GD) has been variable, there are three gestational clusters, which roughly correspond to: early-mid gestation (mice: GD7-9; rats: GD9-11), mid-late gestation (mice: GD10-14; rats: GD12-16) and late gestation (mice: GD15-18; rats: GD18-21).

### 3.4. Candidate gene expression changes in mIA models

The primary outcome measurements of this review, quantitative changes in candidate gene expression, of both RNA and/or protein, were collated from the 118 included studies (Supplement 2). Methodological heterogeneity prevented meta-analysis. Instead, we conducted a qualitative analysis of gene expression. To achieve this, we first collated expression data on all candidate gene studies and thereby identified candidate genes that had been analysed by more than one study. We identified a total of 88 genes (Supplement 4) analysed by more than one study. Using GO analysis, these 88 genes were mapped to 610 biological processes, 71 molecular functions and 74 cellular components (Supplement 5), with the top 50 biological processes displayed in Fig. 5.

These results showed that these candidate genes were primarily associated with neurodevelopment, stress responses, immune responses, cell signalling and metabolism. Using these ontologies as a guide, we clustered genes into three key functional areas: immune/stress responses (Table 1), neurotransmission/neuronal signalling (Table 2) and neurodevelopment (Table 3). It is worth noting that these groupings are not mutually exclusive, with several genes shown to overlap between multiple biological processes.

We next used the data collated for these 88 genes to identify whether any studies presented replicated or conflicting expression data within a given offspring brain tissue for mIA-affected offspring, relative to control offspring. Additionally we assessed if there were any identifiable developmental patterns in expression of these genes in mIA-affected
Fig. 3. Summary of the reported methodological choices across the 118 studies included in the review. Figure summarises the methodological heterogeneity of studies included in the review, from animal strains to immunogen properties and administration procedures across to outcome measurements (including tissue, age and molecular assay). Where numbers are included in brackets this indicates number of studies using a given method. Abbreviations: S. Dawley – Sprague dawley, i.p. – intraperitoneal, i.v. – intravenous, s.c. – subcutaneous, i.n. – intranasal, E – early-mid gestation, M – mid-late gestation, L – late gestation, ACC – Anterior Cingulate Cortex, C. Callousum – Corpus Callousum, Cere. C. – Cerebral cortex, Cing. C. – Cingulate Cortex, CPu – Caudate Putamen, DG – Denate Gyrus, FC – Frontal Cortex, Hipp – Hippocampus, Hypoth. – Hypothalamus, Motor C. – Motor Cortex, Mesenceph. – Mesencephalon, NAc – nucleus accumbens, olf. – olfactory, PFC – Prefrontal Cortex, Pir. C. – Piriform Cortex, Par. C. – Parietal Cortex, PVN – Paraventricular Nucleus, VTA – Ventral Tegmental Area, CB – cerebellum, V. Midbrain – Ventral Midbrain, WB – Whole Brain. NS – not specified.

Fig. 4. Induction timings and brain development. Summarises key developmental processes collated from Clancy et al., 2001, 2007 and Chen et al., 2017 and the embryology database (https://embryology.med.unsw.edu.au). Comparative gestational days are shown for mice, rats and humans. When a gestational day of induction was reported at 0.5, it has been represented as having occurred on that given day, hence these values have been rounded down. For mice and rats the number of studies which used each gestational day is shown for each immunogen. Note that two studies (Ratnayake et al., 2012, 2014) are not included in the data as these studies used the spiny mouse, with a notably longer gestation than an average mouse, lasting 35 days, and performed immune induction at GD20 in the mid-late gestational period.
offspring, relative to controls, across studies, such as persistent increases or decreases from fetal to adult developmental periods. To achieve this, within each tissue, offspring age was divided into the following categories based on pre-natal or post-natal day (P) of offspring age: fetal/pre-natal (F), neonatal (N: P0-1), juvenile (J: P4-24), adolescent/pubescent (P: P28-54), adult (A: P56-8 mo) or aged/old (O: ≥1 y), as specified within the studies. Of note, for the purpose of the studies included in this review, these age ranges were applicable across both mice and rats. Within a tissue and age group, outcome measures were compiled alongside model type (rodent and immunogen) and gestational timing of immune induction.

3.4.1. Immune/stress response gene expression analysis in mLIA-exposed offspring brain tissues

The largest functional group was comprised of 35 genes involved in immune and/or stress responses (Table 1) and subdivided as follows: cytokines (Csf2, Ifng, Il1b, Il2, Il4, Il5, Il6, Il7, Il9, Il12b, Il13, Il17a, Il18, Tnfa, Vegfa), chemokines (Ccl2, Ccl11, Cc15, Cxcl1, Ccl3, Ccl4), corticosteroid signalling (Nr3c1, Nr3c2, Fkbp5), enzymes (Alox12, Arg1, Mmp9, Ptg2), cell surface proteins (Aqp4, Cxcl10, Cx3cr1) and other signalling molecules (Nfkb1, Casp3, Npy). Only one of these, Aqp4, was assessed using an mouse-influenza model.

The three genes involved in corticosteroid signalling, Nr3c1...
Table 1

| GENE (PROTEIN) | TISSUE | AGE | OUTCOME | MODEL | REFERENCES |
|----------------|--------|-----|---------|-------|------------|
| Aloc12 (Alox12) | Whole brain | F | 1h | M-PIC / R-LPS | M-LPS: Liverman et al., 2006<sup>R</sup> |
| | Core Cortex | P | ↑ | R-PIC | M-PIC: Money et al., 2018<sup>R</sup> |
| Arg1 (ARG-1) | Whole brain | F | ↓<sup>SR</sup> | M-PIC | M-LPS: O’Loughlin et al., 2017<sup>R</sup> |
| | F Cortex | J | N<sup>R</sup> | R-PIC | M-LPS: Liverman et al., 2006<sup>R</sup> |
| | Hipp | J | ±<sup>RP</sup> | R-PIC | M-LPS: Liverman et al., 2006<sup>R</sup> |
| Aqp4 (AQP-4) | Neocortex | P / A | ↑<sup>N</sup> / N<sup>RP</sup> | M-INF | M-LPS: Liverman et al., 2006<sup>R</sup> |
| | Hipp | NA / JP | N<sup>R</sup> | M-INF | M-LPS: Liverman et al., 2006<sup>R</sup> |
| | CB | PA | N<sup>P</sup> | M-INF | M-LPS: Liverman et al., 2006<sup>R</sup> |
| Casp3 (CASP-3) | Whole brain | F | 1<sup>th</sup> | R-LPS | M-LPS: Liverman et al., 2006<sup>R</sup> |
| | Hipp | A | N<sup>RP</sup> / 1<sup>R</sup> | R-PIC / R-LPS | M-LPS: Liverman et al., 2006<sup>R</sup> |
| Cd2 (MCP-1) | Whole brain | F | 6h, 12h | M-LPS<sup>LR</sup> | M-LPS: Liverman et al., 2006<sup>R</sup> |
| | F | 24h | ↑ | M-PIC<sup>LR</sup> | M-LPS: Liverman et al., 2006<sup>R</sup> |
| | F | 2<sup>d</sup>, 4d | N<sup>R</sup> | M-LPS<sup>LR</sup> | M-LPS: Liverman et al., 2006<sup>R</sup> |
| | Amygdala | N | N<sup>R</sup> | M-LPS<sup>LR</sup> | M-LPS: Liverman et al., 2006<sup>R</sup> |
| | Hipp | NJ / JPA | N<sup>R</sup> | M-LPS<sup>LR</sup> | M-LPS: Liverman et al., 2006<sup>R</sup> |
| | F Cortex | NJA / JP | N<sup>R</sup> | M-LPS<sup>LR</sup> | M-LPS: Liverman et al., 2006<sup>R</sup> |
| | Cing Cortex | NJA / JP | N<sup>R</sup> | M-LPS<sup>LR</sup> | M-LPS: Liverman et al., 2006<sup>R</sup> |
| Cx3cr1 (C3CR1) | CB | A | N<sup>P</sup> | M-PIC | M-LPS: Liverman et al., 2006<sup>R</sup> |
| | F Cortex | JA | N<sup>P</sup> | R-PIC | M-LPS: Liverman et al., 2006<sup>R</sup> |
| | Hipp | NA | M-PIC | M-LPS: Liverman et al., 2006<sup>R</sup> |
| Cd11 (Eotaxin) | Whole brain | F | 24h | M-LPS<sup>LR</sup> | M-LPS: Liverman et al., 2006<sup>R</sup> |
| | Hipp | NJA / J | N<sup>P</sup> / 1<sup>F</sup> | M-PIC | M-LPS: Liverman et al., 2006<sup>R</sup> |
| | F Cortex | NJA / J | N<sup>P</sup> / 1<sup>F</sup> | M-PIC | M-LPS: Liverman et al., 2006<sup>R</sup> |
| | Cing Cortex | NJA / J | N<sup>P</sup> / 1<sup>F</sup> | M-PIC | M-LPS: Liverman et al., 2006<sup>R</sup> |
| | Hipp | P | N<sup>RP</sup> | M-LPS<sup>LR</sup> | M-LPS: Liverman et al., 2006<sup>R</sup> |
| Fkbp5 (FKBP5) | PFC | A | N<sup>P</sup> | M-PIC | M-LPS: Liverman et al., 2006<sup>R</sup> |
| | Hypoth | P | N<sup>RP</sup> | M-PIC | M-LPS: Liverman et al., 2006<sup>R</sup> |
| | Whole brain | F | 24h | M-LPS<sup>LR</sup> | M-LPS: Liverman et al., 2006<sup>R</sup> |
| | Hipp | NJPA / P | N<sup>P</sup> | M-LPS<sup>LR</sup> | M-LPS: Liverman et al., 2006<sup>R</sup> |
| | F Cortex | NJPA / J | 1<sup>RP</sup> / 1<sup>P</sup> | M-PIC | M-LPS: Liverman et al., 2006<sup>R</sup> |
| | Cing Cortex | NJPA / J | 1<sup>RP</sup> / 1<sup>P</sup> | M-PIC | M-LPS: Liverman et al., 2006<sup>R</sup> |
| | | | 1<sup>RP</sup> / 1<sup>P</sup> | M-PIC | M-LPS: Liverman et al., 2006<sup>R</sup> |
| | Whole brain | F | 6h, 12h | M-LPS<sup>LR</sup> | M-LPS: Liverman et al., 2006<sup>R</sup> |
| | Hipp | J | N<sup>P</sup> | M-LPS<sup>LR</sup> | M-LPS: Liverman et al., 2006<sup>R</sup> |
| Ifng (IFN-γ) | Hipp | NJPA / P | N<sup>P</sup> / 1<sup>R</sup> | M-PIC / R-PIC | M-LPS: Liverman et al., 2006<sup>R</sup> |
| | F Cortex | NJPA / J | N<sup>P</sup> / 1<sup>F</sup> | M-PIC | M-LPS: Liverman et al., 2006<sup>R</sup> |
| | Core Cortex | P | N<sup>P</sup> | R-LPS | M-LPS: Liverman et al., 2006<sup>R</sup> |
| | Cing Cortex | NA / J | 1<sup>RP</sup> / 1<sup>P</sup> | M-PIC | M-LPS: Liverman et al., 2006<sup>R</sup> |
| | | | 1<sup>RP</sup> / 1<sup>P</sup> | M-PIC | M-LPS: Liverman et al., 2006<sup>R</sup> |
| Il1b (IL-1β) | Whole brain | F | 3h | M-LPS<sup>LR</sup> | M-LPS: Liverman et al., 2006<sup>R</sup> |
| | | F | 4h | M-LPS<sup>LR</sup> | M-LPS: Liverman et al., 2006<sup>R</sup> |
| | | F | 6h | M-LPS<sup>LR</sup> | M-LPS: Liverman et al., 2006<sup>R</sup> |

(continued on next page)
| GENETIC LINEAGE | TISSUE | AGE | OUTCOME | MODEL | REFERENCES |
|----------------|--------|-----|---------|-------|------------|
| **Whole brain** | F – 6h | N⁰ | R-LPS | M-LPS | M-LPS: Liverman et al., 2006⁴ |
| | F – 12h | N⁰ | R-LPS | M-LPS | M-LPS: Liverman et al., 2006⁴ R-LPS: Simões et al., 2018⁶ Gayle et al., 2004⁶⁵ |
| | F – 24h | N⁰ / R⁶ | R-LPS⁵ M-PIC⁵ / R-LPS⁵ M-PIC⁵ | R-LPS⁵ | M-LPS: Liverman et al., 2006⁴ Gayle et al., 2004⁶⁵ M-PIC: Arruda-Brunes and Bruner, 2012⁷ R-PIC: McColl and Pique-Miller, 2019⁸ |
| | F – 2d | N⁰ | R-PIC⁴ M-PIC⁴ | R-PIC⁴ | M-PIC: McColl and Pique-Miller, 2019⁸ M-PIC: Garcia-Valtanan et al., 2020⁶¹ |
| | F – 4d | N⁰ | R-LPS | M-LPS | M-LPS: O’Loughlin et al., 2019⁸ |

**Mesenceph**

| TISSUE | AGE | OUTCOME | MODEL | REFERENCES |
|--------|-----|---------|-------|------------|
| F Cortex | NJA / JP | N⁰ | R-LPS | Garay et al., 2013⁹ |
| | NJA / JP | N⁰ | R-LPS | Ling et al., 2002⁴⁶ |
| Hipp | N⁰ | M-PIC | Garay et al., 2013⁹ |
| | N⁰ | M-PIC | Garay et al., 2013⁹ |
| Amygdala | N⁰ | M-PIC | Garay et al., 2013⁹ |
| | M-PIC | Garay et al., 2013⁹ |
| Cing Cortex | N⁰ | M-PIC | Garay et al., 2013⁹ |

**Amygdala**

| TISSUE | AGE | OUTCOME | MODEL | REFERENCES |
|--------|-----|---------|-------|------------|
| Hipp | A | N⁰ / R⁶ | M-PIC⁵ / M-PIC⁵ R-LPS | M-PIC: Garay et al., 2013⁹ Hui et al., 2018⁸ Gotelli et al., 2015⁵ R-PIC: Ding et al., 2019⁷⁵ Talukdar et al., 2020⁸⁲ |
| | O | N⁰ | M-PIC | Garay et al., 2019⁵⁸ |
| | P | R-PIC | Garay et al., 2019⁵⁸ |
| | A | N⁰ | M-PIC | Willi et al., 2013⁷⁵ R-PIC: Ding et al., 2019⁷⁵ |
| | A | M-PIC | O’Loughlin et al., 2013⁷⁵ |

**Striatum**

| TISSUE | AGE | OUTCOME | MODEL | REFERENCES |
|--------|-----|---------|-------|------------|
| Whole brain | F – 6h | N⁰ | R-LPS | M-PIC: Garay et al., 2013⁹ R-PIC: Chamera et al., 2020⁷⁵ |
| | F – 12h | N⁰ | R-LPS | M-PIC: Garay et al., 2013⁹ R-PIC: Chamera et al., 2020⁷⁵ |
| | F – 24h | N⁰ | R-LPS | M-PIC: Garay et al., 2013⁹ R-PIC: Chamera et al., 2020⁷⁵ |
| | F – 12h | N⁰ | R-LPS | M-PIC: Garay et al., 2013⁹ R-PIC: Chamera et al., 2020⁷⁵ |
| | F – 2d | N⁰ | R-LPS | M-PIC: Garay et al., 2013⁹ R-PIC: Chamera et al., 2020⁷⁵ |
| | N⁰ | M-PIC | M-PIC: Garay et al., 2013⁹ R-PIC: Chamera et al., 2020⁷⁵ |
| | J | N⁰ / N⁰ | M-PIC / R-PIC | M-PIC: Garay et al., 2013⁹ R-PIC: Chamera et al., 2020⁷⁵ |

**Cing Cortex**

| TISSUE | AGE | OUTCOME | MODEL | REFERENCES |
|--------|-----|---------|-------|------------|
| Whole brain | F – 6h | N⁰ | R-LPS | M-PIC: Garay et al., 2013⁹ R-PIC: Chamera et al., 2020⁷⁵ |
| | F – 12h | N⁰ | R-LPS | M-PIC: Garay et al., 2013⁹ R-PIC: Chamera et al., 2020⁷⁵ |
| | F – 24h | N⁰ | R-LPS | M-PIC: Garay et al., 2013⁹ R-PIC: Chamera et al., 2020⁷⁵ |
| | F – 1h | N⁰ | M-LPS | M-LPS: Liverman et al., 2006⁴ R-LPS: Gayle et al., 2004⁶⁵ |
| | F – 2h | N⁰ | M-LPS⁵ | M-LPS⁵ R-LPS⁵ M-PIC⁵ | M-LPS: Liverman et al., 2006⁴ R-LPS: Gayle et al., 2004⁶⁵ |
| | F – 3h | N⁰ | M-LPS⁵ | M-PIC⁵ | M-LPS: Liverman et al., 2006⁴ R-LPS: Gayle et al., 2004⁶⁵ R-PIC: Oskvig et al., 2012⁶⁵ Ginsberg et al., 2018⁶⁵ Dabbah-Assadi et al., 2019⁶⁵ |
| | F – 6h | N⁰ | M-PIC⁵ | M-PIC⁵ M-LPS⁵ R-LPS⁵ M-PIC⁵ | M-LPS: Liverman et al., 2006⁴ R-LPS: Gayle et al., 2004⁶⁵ R-PIC: Oskvig et al., 2012⁶⁵ Ginsberg et al., 2018⁶⁵ Dabbah-Assadi et al., 2019⁶⁵ |

(continued on next page)
Table 1 (continued)

| GENE | TISSUE | AGE | OUTCOME | MODEL | REFERENCES |
|------|--------|-----|---------|-------|------------|
| –(PROTEIN) | | | | | |
| F – 8h | Np | M-LPS |
| F – 12h | tP / Np | M-LPS; R-LPS; R-RIC | M-LPS: Liu et al., 2006R |
| F – 24h | tP / Np | M-LPS; R-LPSR; R-RIC |
| F – 2d | P | R-PIC/M; M-PIC |
| F – 4d | Np | M-PIC |
| 6d | N | M-LPS |
| P | R-PIC/M; M-PIC |
| A | tP / tP | M-PIC |
| F Cortex | Np / Np | M-PIC |
| P | tP | M-PIC |
| Cing Cortex | Np | M-PIC |
| Striatum | N | M-PIC |
| SN | Np | M-PIC |
| P | tP | M-PIC |
| A | Np / tP | M-PIC |
| F – 6h | Np | M-PIC; R-LPS |
| F – 12h | Np | M-LPS |
| F – 24h | Np | M-LPS |
| Whole | brain 24h | Np | M-PIC |
| Hipp | Np / Np | M-PIC |
| P | tP | M-PIC |
| Cing Cortex | Np | M-PIC |
| Amygdala | N | M-PIC |
| F Cortex | Np / tP | M-PIC |
| Cing Cortex | Np | M-PIC |
| F – 1h | Np | R-LPS |
| F – 3h | tP / Np | M-PIC/M; M-PIC |
| F – 4h | Np | M-LPS |
| Whole | brain 12h | Np | M-PIC |
| F – 2d | Np | M-PIC |
| F – 4d | tP | M-PIC |
| F – 6d | Np | M-PIC |
| Amygdala | Np | M-LPS |
| Hipp | Np / tP | M-PIC |
| P | tP | M-PIC |
| P | tP | M-PIC |
| Cing Cortex | Np | M-PIC |
| Whole | brain 2d | tP | M-PIC |
| F Cortex | Np | M-PIC |
| Cing Cortex | Np / tP | M-PIC |
| (IL-10) | | | | | |
| Amgydala | N | M-LPS |
| F Cortex | Np | M-PIC |
| Cing Cortex | Np | M-PIC |
| Whole | brain 2d | tP | M-PIC |
| F Cortex | Np | M-PIC |
| Cing Cortex | Np / tP | M-PIC |
| (IL-12p40) | | | | | |
| | | | | | |

*(Accepted for publication)*
Table 1

| GENETIC ELEMENTS | TISSUE | AGE | OUTCOME | MODEL | INDUCTION TIME | REFERENCES |
|------------------|--------|-----|---------|-------|---------------|------------|
| Nr3c1            | Whole  | F – 6h | N<sup>p</sup> | M-PIC | E – early | Garay et al., 2013<sup>p</sup> |
|                  | brain  | F – 24h | N<sup>p</sup> | M-PIC | E – mid | Arrode-Brusés and Brusés, 2012<sup>p</sup> |
|                  | Hipp   | NJPA  | N<sup>p</sup> | M-PIC | E – mid | Arrode-Brusés and Brusés, 2012<sup>p</sup> |
|                  | Cing Cortex | NJPA  | N<sup>p</sup> | M-PIC | E – mid | Arrode-Brusés and Brusés, 2012<sup>p</sup> |
| Mmp9             | Whole  | F – 6h | t<sup>p</sup> | M-PIC | R-LPS | R-LPS: Simões et al., 2018<sup>p</sup> M-PIC: Garcia-Valtanen et al., 2020<sup>p</sup> |
|                  | brain  | F – 24h | t<sup>p</sup> | M-PIC | R-LPS | R-LPS: Simões et al., 2018<sup>p</sup> M-PIC: Garcia-Valtanen et al., 2020<sup>p</sup> |
|                  | F – 24h | N<sup>p</sup> | M-PIC | R-LPS | R-LPS: Simões et al., 2018<sup>p</sup> M-PIC: Garcia-Valtanen et al., 2020<sup>p</sup> |
|                  | F – 6h | N<sup>p</sup> | M-PIC | R-LPS | R-LPS: Simões et al., 2018<sup>p</sup> M-PIC: Garcia-Valtanen et al., 2020<sup>p</sup> |
|                  | SN    | A     | N<sup>R</sup> | M-PIC | R-LPS | Purves-Tyson et al., 2019<sup>R</sup> |
|                  | Whole  | F – 24h | N<sup>p</sup> | M-PIC | R-LPS | Arrode-Brusés and Brusés, 2012<sup>p</sup> |
|                  | F – 24h | N<sup>p</sup> | M-PIC | R-LPS | R-LPS: Simões et al., 2018<sup>p</sup> M-PIC: Garcia-Valtanen et al., 2020<sup>p</sup> |
|                  | F – 24h | N<sup>p</sup> | M-PIC | R-LPS | R-LPS: Simões et al., 2018<sup>p</sup> M-PIC: Garcia-Valtanen et al., 2020<sup>p</sup> |
|                  | F – 24h | N<sup>p</sup> | M-PIC | R-LPS | R-LPS: Simões et al., 2018<sup>p</sup> M-PIC: Garcia-Valtanen et al., 2020<sup>p</sup> |

(continued on next page)
### Table 1 (continued)

| GENE (PROTEIN) | TISSUE | AGE | OUTCOME | MODEL | INDUCTION TIME | REFERENCES |
|----------------|--------|-----|---------|-------|----------------|------------|
| Ptg2 (COX-2)  | Hipp   | F – 4h, F – 4d, 6d | N<sup>R</sup> | M-LPS | O’Loughlin et al., 2019<sup>R</sup> |
| Amygdala CB   | A      | N<sup>R</sup> | M-LPS | Hu et al., 2018<sup>R</sup> |
|                | P      | N<sup>R</sup> | M-LPS | M-PIC: Hui et al., 2018<sup>R</sup> (A only) R-LPS: Cieslik et al., 2020<sup>R</sup> (P only) |
|                | F      | 1h<sup>/<sup>N</sup> / N<sup>R</sup> | R-LPS<sup>S</sup>, R-LPS<sup>M</sup> | M-LPS: Liverman et al., 2006<sup>R</sup> R-LPS: Gayle et al., 2004<sup>R</sup> |
|                | F      | 2h<sup>/N</sup> | R-LPS<sup>M</sup>, R-PIC<sup>M</sup> | M-LPS: Liverman et al., 2006<sup>R</sup> R-LPS: Urakubo et al., 2003<sup>R</sup> M-PIC: Ratnayake et al., 2014<sup>R</sup> R-PIC: Gilmore et al., 2005<sup>R</sup> |
|                | F      | 3h<sup>/N</sup> | R-PIC<sup>M</sup>, R-PIC<sup>2</sup> | M-PIC: Meyer et al., 2006<sup>R</sup> |
|                | F      | 4h<sup>/N</sup> | R-LPS<sup>M</sup>, R-LPS<sup>M</sup>, M-PIC<sup>M</sup>, R-PIC<sup>M</sup> | M-LPS: Liverman et al., 2006<sup>R</sup> R-LPS: O’Loughlin et al., 2017<sup>R</sup> R-LPS: Oskvig et al., 2012<sup>R</sup> |
| Whole brain   | N      | N<sup>R</sup> | M-LPS<sup>S</sup> | M-LPS: Liverman et al., 2006<sup>R</sup> R-LPS: Simoes et al., 2018<sup>R</sup> Gayle et al., 2004<sup>R</sup> M-PIC: Meyer et al., 2006<sup>R</sup> R-PIC: McColl and Piquette-Miller, 2015<sup>R</sup> Gilmore et al., 2005<sup>R</sup> |
| Tnfa (TNFα)   | J      | N<sup>R</sup> / i<sup>P</sup> | M-PIC R-PIC<sup>M</sup>, R-PIC<sup>M</sup> | R-PIC: Gilmore et al., 2005<sup>R</sup> R-PIC: Garay et al., 2013<sup>R</sup> |
|                | PA     | N<sup>P</sup> | M-PIC | Zhao et al., 2019<sup>P</sup> |
|                | P      | N<sup>P</sup> | R-PIC | Ling et al., 2002<sup>P</sup> |
|                | J      | N<sup>P</sup> | R-LPS | Zhao et al., 2019<sup>P</sup> |
|                | F      | N<sup>P</sup> | R-PIC | Ding et al., 2019<sup>P</sup> |
| PFC            | A      | N<sup>P</sup> | R-PIC | Ding et al., 2019<sup>R</sup> R-PIC: Willi et al., 2013<sup>R</sup> |
|                | N      | N<sup>P</sup> | M-PIC | Zhao et al., 2019<sup>P</sup> |
| Hipp           | J      | N<sup>P</sup> | M-PIC | Garay et al., 2013<sup>P</sup> |
|                | P      | N<sup>P</sup> | M-PIC | M-PIC: Garay et al., 2013<sup>R</sup> R-PIC: Chamera et al., 2020<sup>R</sup> R-PIC: M-PIC: Garay et al., 2013<sup>R</sup> |
| Amygdala CB    | O      | N<sup>P</sup> | M-PIC | Giovannoli et al., 2015<sup>M</sup> Garay et al., 2013<sup>R</sup> |
| Cing Cortex    | P      | N<sup>P</sup> | R-LPS | Giovannoli et al., 2015<sup>M</sup> |
| Striatum       | A      | N<sup>P</sup> | M-PIC | Cieslik et al., 2020<sup>M</sup> |
| SN             | O      | N<sup>P</sup> | M-LPS | Garay et al., 2013<sup>P</sup> |
|                | O      | N<sup>P</sup> | M-LPS | Purves-Tyson et al., 2014<sup>R</sup> |
|                | F      | 1h, 2h | N<sup>R</sup> | M-LPS<sup>L</sup> | M-LPS: Liverman et al., 2006<sup>R</sup> |
|                | F      | 3h<sup>/N</sup> | i<sup>P</sup> | R-PIC<sup>M</sup> | M-PIC: Money et al., 2018<sup>R</sup> |
|                | F      | 4h<sup>/N</sup> | i<sup>P</sup> | R-PIC<sup>M</sup> | M-LPS: Liverman et al., 2006<sup>R</sup> |
| Whole brain    | F      | 6h<sup>/N</sup> | M-PIC<sup>M</sup>, M-LPS<sup>M</sup>, M-PIC<sup>M</sup> | M-PIC: Arrode-Bruises and Brües, 2012<sup>R</sup> Openshaw et al., 2019<sup>R</sup> M-LPS: Liverman et al., 2006<sup>R</sup> |
|                | A      | i<sup>P</sup> | M-PIC | Khan et al., 2014<sup>R</sup> |

Compiled immune/stress response gene expression changes in mIA models. Within a row forward slashes have been used to separate different outcome data within the same tissue at different timings and/or within different methodologies and align across the row in each column. Where the same tissue/timepoint has been analysed by more than one model type, the references relevant to the given models are indicated in the final column, along with whether the study performed protein/RNA analysis, single sex analysis and whether they validated mIA. **Tissue abbreviations:** Hipp – Hippocampus; PFC – Prefrontal Cortex; CB – Cerebellum; Cing Cortex – Cingulate Cortex; F Cortex – Frontal Cortex; SN – Substantia Negra; Cere Cortex – Cerebral Cortex; Hypoth – Hypothalamus; PV Nucleus – Paraventricular Nucleus. **Age abbreviations:** F - Fetal; N - Neonate; J - Juvenile; P - Adolescent/Pubescent; A - Adult; O - Aged/Old; h - hours post maternal immune induction; d – days post maternal immune induction. **Outcome abbreviations:** N - no change; ↑ - increase; ↓ - decrease. **Model abbreviations:** M-IFN – mouse-influenza; M-PIC – mouse-poly(I:C); R-PIC – rat-poly(I:C); M-LPS – mouse-LPS; R-LPS – rat-LPS. Gestational induction timeframe for mIA models has been indicated only for analyses in tissues where outcome measure varies with gestational timing of immune induction.

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### Table 2

Neurotransmission signalling gene expression changes in mLN offspring relative to controls.

| GENE (PROTEIN) | TISSUE | AGE | OUTCOME Protein; RNA^R | MODEL Induction time: E – early-mid; M – mid-late; L – late | REFERENCES |
|---------------|--------|-----|------------------------|-------------------------------------------------|------------|
| Gad2 (GAD65)  | Whole  | NA  | N^P / ↑P              | M-INF                                           | Fatemi et al., 2004^P |
|               | CB     | NJA | N^P / ↑P              | M-INF                                           | Fatemi et al., 2017^F,PM |
|               | P      | P   | N^P / ↑P              | M-INF                                           | Richetto et al., 2014^F,PM |
|               | PFC    | A   | ↑P                    | M-INF                                           | Richetto et al., 2014^F,PM |
|               | Cere   | A   | N^R                  | R-PIC                                           | Labouesse et al., 2015^R |
|               | Cortex | B   | F / N                | M-PIC                                           | Duchatel et al., 2019^R |
|               | Forebrain | F | I^P / N^R               | R-PIC                                           | Pratt et al., 2013^R |
|               | Whole  | F   | N^R                  | R-LPS; M-PIC                                     | Dabbah-Assadi et al., 2014^R |
|               | brain  | F   | N^P / ↑P              | M-INF                                           | Fatemi et al., 2004^P |
|               | PA     | J   | I^P / ↑R              | M-PIC / R-PIC                                   | M-PIC: Tang et al., 2013^RM, R-PIC: Cassella et al., 2016^RM |
|               | Hipp   | A   | I^P (PD-HIPP); ↓P     | M-PIC R-PIC / R-PIC                             | R-PIC: Cassella et al., 2016^RM |
|               |        | J   | N^R                  | R-PIC                                           | M-PIC: Cassella et al., 2016^RM |
|               | PFC    | P   | I^P / N^RP            | M-PIC_R^P / M-PIC_R-PIC                         | M-PIC: Deslauriers et al., 2013^RM, R-PIC: Cassella et al., 2016^RM |
| Gad1 (GAD67)  | F Cortex | JPA | N^R              | R-PIC                                           | Fatemi et al., 2017^F,PM |
|               | CB     | NJA | N^P / P               | M-INF                                           | Cassella et al., 2016^RM |
|               | Par Cortex | JPA | N^P              | R-PIC                                           | Cassella et al., 2016^RM |
|               | Pir Cortex | JPA | N^P              | R-PIC                                           | Cassella et al., 2016^RM |
|               | Striatum | JPA | N^P                  | M-PIC R-PIC                                     | M-PIC: Tang et al., 2013^RM, R-PIC: Cassella et al., 2016^RM |
|               | Thalamus | JP   | A / N^P / ↑P          | R-PIC                                           | Cassella et al., 2016^RM |
|               | Cere   | J   | N^P                  | M-PIC                                           | Tang et al., 2013^RM |
|               | Cortex | A   | N^P                  | R-PIC                                           | M-PIC: Tang et al., 2013^RM, R-PIC: Cassella et al., 2016^RM |
|               | B      | F   | N^R                  | M-PIC                                           | Pratt et al., 2013^R |
|               | Forebrain | CB | NJPA                | M-INF                                           | Fatemi et al., 2017^F,PM |
|               | Hipp   | A   | N^P (PD-HIPP); ↓P     | M-PIC                                           | Richetto et al., 2015^RM |
|               |        |      |                     |                                                | Richetto et al., 2014^RM, R-PIC: Cassella et al., 2016^RM |
| Gabra1 (GABAa1) | PFC  | A   | ↑P                    | M-PIC_R^P / R-PIC                                 | Pratt et al., 2013^R |
|               | Striatum | A   | N^P                  | M-PIC                                           | Money et al., 2018^R |
|               | B      | F   | I^P                  | M-PIC                                           | Fatemi et al., 2017^F,PM |
|               | Forebrain | CB | NJPA                | M-INF                                           | Richetto et al., 2015^RM |
|               | Hipp   | A   | N^P (PD-HIPP); ↓P     | M-PIC                                           | Nyffeler et al., 2006^P |
| Gabra2 (GABAa2) | PFC  | P   | I^P / ↑P              | M-PIC_R^P / R-PIC                                 | Richetto et al., 2014^RM, R-PIC: Cassella et al., 2016^RM |
|               | Striatum | A   | N^P                  | M-PIC                                           | Richetto et al., 2014^RM, R-PIC: Cassella et al., 2016^RM |
|               | Amygdala | A | ↑P                  | M-PIC                                           | Nyffeler et al., 2006^P |
| Gabra3 (GABAa3) | PFC  | A   | N^P                  | M-PIC_R^P / R-PIC                                 | Richetto et al., 2014^RM, R-PIC: Cassella et al., 2016^RM |
|               | Striatum | A   | N^P                  | M-PIC_R^P / R-PIC                                 | Richetto et al., 2014^RM, R-PIC: Cassella et al., 2016^RM |
|               | Hipp   | A   | N^P                  | M-PIC                                           | Richetto et al., 2015^RM |
| Gabra4 (GABAa4) | PFC  | P / A | ↑P / ↑P          | M-PIC_R^P / M-PIC                                 | Richetto et al., 2014^RM, R-PIC: Cassella et al., 2016^RM |
|               | Striatum | A   | N^P                  | M-PIC_R^P / R-PIC                                 | Richetto et al., 2014^RM, R-PIC: Cassella et al., 2016^RM |
|               | CB     | NJPA | N^P                  | M-INF                                           | Fatemi et al., 2017^F,PM |
| Gabra5 (GABAa5) | PFC  | P / A | ↑P / ↑P          | M-PIC_R^P / R-PIC                                 | Richetto et al., 2014^RM, R-PIC: Cassella et al., 2016^RM |
|               | Striatum | A   | N^P                  | M-PIC_R^P / R-PIC                                 | Richetto et al., 2014^RM, R-PIC: Cassella et al., 2016^RM |
|               | Hipp   | A   | N^P                  | M-PIC                                           | Pratt et al., 2013^R |
|               | Whole brain | F | I^P                  | M-PIC                                           | Money et al., 2018^R |
| Drd1 (D1R)    | HIPP   | A   | N^P                  | M-PIC_R^P / R-PIC                                 | Fatemi et al., 2017^F,PM |
|               | PFC    | A   | N^P                  | M-PIC_R^P / R-PIC                                 | Buschert et al., 2014^RM, Meyer et al., 2008^P |
|               | Striatum | A   | N^P                  | R-LPS; M-PIC                                     | Buschert et al., 2014^RM, Meyer et al., 2008^P, Vuillermot et al., 2012^F,PM |
|               | Off Bulb | A   | N^P                  | R-LPS; M-PIC                                     | Kirsten et al., 2012^RM, M-PIC: Vuillermot et al., 2012^F,PM |
|               | NAc    | A   | I^P / N^P            | R-PIC_R^P / R-PIC_1                                 | Kirsten et al., 2011^F,PM |
|               | SN     | A   | N^P                  | R-PIC_R^P / R-PIC                                 | Meehan et al., 2017^RM |
|               | VTA    | A   | N^P                  | R-PIC                                           | Meehan et al., 2017^RM |

(continued on next page)
Table 2 (continued)

| GENE (PROTEIN) | TISSUE | AGE | OUTCOME Protein\(^2\); RNA\(^2\) | MODEL Induction time: E – early-mid; M – mid-late; L – late | REFERENCES |
|---------------|--------|-----|---------------------------------|-------------------------------------------------|------------|
| Drd2 (D2R)    |       |     |                                 |                                                 |            |
|       |       |     |                                 |                                                 |            |
|       |       |     |                                 |                                                 |            |

| Th (TH)       |       |     |                                 |                                                 |            |
|---------------|--------|-----|---------------------------------|-------------------------------------------------|------------|
|               |        |     |                                 |                                                 |            |
|               |        |     |                                 |                                                 |            |

| Slt6a3 (DAT)  |       |     |                                 |                                                 |            |
|---------------|--------|-----|---------------------------------|-------------------------------------------------|------------|
|               |        |     |                                 |                                                 |            |
|               |        |     |                                 |                                                 |            |

| Comt (COMT)   |       |     |                                 |                                                 |            |
|---------------|--------|-----|---------------------------------|-------------------------------------------------|------------|
|               |        |     |                                 |                                                 |            |
|               |        |     |                                 |                                                 |            |

| Slt1a3 (EAAT1)|       |     |                                 |                                                 |            |
|---------------|--------|-----|---------------------------------|-------------------------------------------------|------------|
|               |        |     |                                 |                                                 |            |
|               |        |     |                                 |                                                 |            |

| Slt1a2 (EAAT2)|       |     |                                 |                                                 |            |
|---------------|--------|-----|---------------------------------|-------------------------------------------------|------------|
|               |        |     |                                 |                                                 |            |
|               |        |     |                                 |                                                 |            |

| Slt1a1 (EAAT3)|       |     |                                 |                                                 |            |
|---------------|--------|-----|---------------------------------|-------------------------------------------------|------------|
|               |        |     |                                 |                                                 |            |
|               |        |     |                                 |                                                 |            |

| Grin1 (NR1)   |       |     |                                 |                                                 |            |
|---------------|--------|-----|---------------------------------|-------------------------------------------------|------------|
|               |        |     |                                 |                                                 |            |
|               |        |     |                                 |                                                 |            |

| Grin2a (NR2A)|       |     |                                 |                                                 |            |
|---------------|--------|-----|---------------------------------|-------------------------------------------------|------------|
|               |        |     |                                 |                                                 |            |
|               |        |     |                                 |                                                 |            |

(continued on next page)
| GENE (PROTEIN) | TISSUE | AGE | OUTCOME | OUTCOME Protein; RNA<sup>R</sup> | MODEL | Induction time: E – early-mid; M – mid-late; L – late | REFERENCES |
|----------------|--------|-----|--------|-----------------|-------|-------------------------------------------------|-------------|
| NGF (TRKB)     | Hipp   | J   | ↑      | A N<sup>R</sup> | R-PIC | R-PIC                                           | Hao et al., 2019<sup>RPM</sup> |
|                | Pirc   | J   | ↑      | A N<sup>R</sup> | R-PIC | R-PIC                                           | Rahman et al., 2017<sup>RM</sup> |
|                | Cere   | A   | ↑      | N<sup>R</sup> | R-PIC | R-PIC                                           | Rahman et al., 2017<sup>RM</sup> |
|                | Cortex | A   | ↑      | N<sup>R</sup> | R-PIC | R-PIC                                           | Rahman et al., 2017<sup>RM</sup> |
|                | Hipp   | J   | ↓      | A N<sup>R</sup> | R-PIC | R-PIC / R-LPS                                   | Hao et al., 2019<sup>RPM</sup> |
|                | Pirc   | J   | ↑      | A N<sup>R</sup> | R-PIC | R-PIC / R-LPS                                   | Hao et al., 2019<sup>RPM</sup> |
|                | Cere   | A   | ↑      | N<sup>R</sup> | R-PIC | R-PIC / R-LPS                                   | Hao et al., 2019<sup>RPM</sup> |
|                | Cortex | A   | ↑      | N<sup>R</sup> | R-PIC | R-PIC / R-LPS                                   | Hao et al., 2019<sup>RPM</sup> |
|                | Hipp   | J   | ↑      | A N<sup>R</sup> | R-PIC | R-PIC / R-LPS                                   | Hao et al., 2019<sup>RPM</sup> |
|                | Pirc   | J   | ↑      | A N<sup>R</sup> | R-PIC | R-PIC / R-LPS                                   | Hao et al., 2019<sup>RPM</sup> |
|                | Cere   | A   | ↑      | N<sup>R</sup> | R-PIC | R-PIC / R-LPS                                   | Hao et al., 2019<sup>RPM</sup> |
|                | Cortex | A   | ↑      | N<sup>R</sup> | R-PIC | R-PIC / R-LPS                                   | Hao et al., 2019<sup>RPM</sup> |
|                | Hipp   | J   | ↑      | A N<sup>R</sup> | R-PIC | R-PIC / R-LPS                                   | Hao et al., 2019<sup>RPM</sup> |
|                | Pirc   | J   | ↑      | A N<sup>R</sup> | R-PIC | R-PIC / R-LPS                                   | Hao et al., 2019<sup>RPM</sup> |
|                | Cere   | A   | ↑      | N<sup>R</sup> | R-PIC | R-PIC / R-LPS                                   | Hao et al., 2019<sup>RPM</sup> |
|                | Cortex | A   | ↑      | N<sup>R</sup> | R-PIC | R-PIC / R-LPS                                   | Hao et al., 2019<sup>RPM</sup> |
|                | Hipp   | J   | ↑      | A N<sup>R</sup> | R-PIC | R-PIC / R-LPS                                   | Hao et al., 2019<sup>RPM</sup> |
|                | Pirc   | J   | ↑      | A N<sup>R</sup> | R-PIC | R-PIC / R-LPS                                   | Hao et al., 2019<sup>RPM</sup> |
|                | Cere   | A   | ↑      | N<sup>R</sup> | R-PIC | R-PIC / R-LPS                                   | Hao et al., 2019<sup>RPM</sup> |
|                | Cortex | A   | ↑      | N<sup>R</sup> | R-PIC | R-PIC / R-LPS                                   | Hao et al., 2019<sup>RPM</sup> |
|                | Hipp   | J   | ↑      | A N<sup>R</sup> | R-PIC | R-PIC / R-LPS                                   | Hao et al., 2019<sup>RPM</sup> |
|                | Pirc   | J   | ↑      | A N<sup>R</sup> | R-PIC | R-PIC / R-LPS                                   | Hao et al., 2019<sup>RPM</sup> |
|                | Cere   | A   | ↑      | N<sup>R</sup> | R-PIC | R-PIC / R-LPS                                   | Hao et al., 2019<sup>RPM</sup> |
|                | Cortex | A   | ↑      | N<sup>R</sup> | R-PIC | R-PIC / R-LPS                                   | Hao et al., 2019<sup>RPM</sup> |

*continued on next page*
Compiled neurotransmission gene expression changes in mIA models. Within a row forward slashes have been used to separate different outcome data within the same tissue at different timings and/or within different methodologies, and align across the row in each column. Where the same tissue/timepoint has been analysed by more than one model type, the references relevant to the given models are indicated in the final column, along with whether the study performed protein/RNA analysis, single sex analysis and whether they validated mIA.

**Tissue abbreviations:** Hipp – Hippocampus; PFC – Prefrontal Cortex; CB – Cerebellum; F – Frontal Cortex; SN – Substantia Nigra; Cere Cortex – Cerebral Cortex; ACC – Anterior Cingulate Cortex, B Forebrain – Basal Forebrain; Par Cortex – Parietal Cortex; Pir Cortex – Piriform Cortex; Hypoth – Hypothalamus; Olf Bulb – Olfactory Bulb; VTA – Ventral Tegmental Area; CPH – Caudate Putamen; NAC – Nucleus Accumbens; Y Midbrain – Ventral Midbrain.

**Age abbreviations:** F - Fetal; N – Neonate; J – Juvenile; P – Adolescent/Pubescent; A – Adult; O – Aged/Old; h – hours post immune induction; d – days post immune induction.

**Model abbreviations:** M – Mouse; PIC – Poly(I:C); LPS – Lipopolysaccharide; h – hours post immune induction; d – days post immune induction.

Table 2 (continued)

| GENE (PROTEIN) | TISSUE | AGE | OUTCOME | MODEL | INDUCTION TIME: | REFERENCES |
|---------------|--------|-----|---------|-------|-----------------|------------|
| F Cortex      | JPA    | NR  | R-PIC   |       |                 | Hemmerle et al., 2015*RM |
| ACC Cortex    | JPA    | NR  | R-PIC   |       |                 | Hemmerle et al., 2015*RM |
| Pari Cortex   | JPA    | NR  | R-PIC   |       |                 | Hemmerle et al., 2015*RM |
| Pin Cortex    | J/PA   | h   | R-PIC   |       |                 | Hemmerle et al., 2015*RM |
| Striatum      | A/JP   | h   | R-PIC   |       |                 | Hemmerle et al., 2015*RM |

**Notes:** R.M. Woods et al. 2021 | Neurobiology and Biobehavioral Reviews 129 (2021) 389–421 | 403 | 389–421

(gluocorticoid receptor), Nr3c2 (mineralocorticoid receptor) and Fkbp5 (FK506 binding protein 51, regulator of glucocorticoid receptor sensitivity) showed limited inter-study overlap in tissues analysed and most results were non-significant. Exceptions to this were increased Nr3c2 expression in the adult hippocampus in female mIA-offspring (Ronovsky et al., 2017) and increased Nr3c1 expression in the adult prefrontal cortex (PFC) and hippocampus (Buschert et al., 2016) in mouse-poly(I:C) models and decreased Nr3c1 expression in the adult dorsal hippocampus in a rat-LPS model (Lin et al., 2012). Of interest, Fkbp5 expression changes in mIA-offspring was sex-specific in a rat-LPS model (Novoñez-Estevéz et al., 2020), with expression decreased in both the adolescent hippocampus and hypothalamus in female mIA-affected offspring whereas expression was decreased and unchanged, respectively, in male mIA-affected offspring.

The majority of genes within the immune/stress response group were chemokines and cytokines. However, most of these genes have only been analysed by a single study in a given tissue at a specific developmental timepoint. Across mIA-models, fetal whole brain was analysed at a specific time post-mIA induction for numerous immune/stress response genes, with several demonstrating significant expression changes varying temporally across models (Table 1). Further, from work by Smith and colleagues, maternal IL-6 has been widely accepted as critical for mediating the effects of mIA on neurodevelopmental outcomes (Smith et al., 2007). This may explain the dominance of Il6 expression relative to other immune function genes. Ten offspring tissues have been analysed for Il6 expression, with four tissues (striatum, PFC, hippocampus and fetal whole brain) investigated in more than one study and/or mIA-model (Table 1). Within offspring tissues, studies have shown predominantly significant increases in Il6 expression in mIA-offspring, although non-significant changes, dependent on tissue and developmental timepoint, have also been reported (Table 1). Notably, only one study demonstrated a reduction in Il6 expression in mIA-affected offspring and only in the adolescent hippocampus, frontal and cingulate cortex and juvenile cingulate cortex (Garay et al., 2013). In the hippocampus, Il6 expression has been shown in a majority of studies, to be significantly elevated in mA-exposed offspring from fetal through to adult developmental time points (Ding et al., 2019; Garay et al., 2013; Merti et al., 2017; Talukdar et al., 2020; Tang et al., 2013; Zhao et al., 2019). Further, the data from hippocampal analyses demonstrated that these results were in part dependent on gestational timing of mIA induction and model type, particularly well demonstrated in the adolescent hippocampal tissue, where rat-poly(I:C) models showed increased Il6 expression while mouse-poly(I:C) models showed both decreased and non-significant changes in expression (Ding et al., 2019; Garay et al., 2013; Giovanoli et al., 2015, 2016; Zhao et al., 2019). Fewer studies have investigated the striatum, PFC, cerebral and frontal cortices, with less overlap in developmental timepoint between studies. Where such overlaps occurred, no significant changes in Il6 expression were observed in the adult striatum in two mouse-poly(I:C) models (Tang et al., 2013; Willi et al., 2013). By contrast, in the adult PFC and juvenile frontal cortex, Il6 expression was increased in rat-poly(I:C) models (Chamera et al., 2020; Ding et al., 2019), and non-significant in mouse-poly(I:C) models (Garay et al., 2013; Willi et al., 2013), thereby demonstrating marked differences between both tissue and models.

Tnfa, Il1b and Il10 have also been investigated, widely, with both Tnfa and Il1b analysed in eleven tissues and Il10 in five tissues. Changes in expression of these three cytokines were found to be more diverse than those demonstrated for Il6, with studies showing increases, decreases and non-significant changes in expression across tissues and developmental stages. In contrast to Il6, several studies reported reductions in expression of Il10, Il1b and Tnfa in various tissues (Table 1). Notably, across all tissues, those studies showing decreased expression of Tnfa, Il1b or Il10 almost exclusively used poly(I:C). Indeed, only one LPS model, using rats (Urakubo et al., 2001), showed decreased Tnfa expression in the fetal whole brain 2 h post-mIA induction and only at the higher dose of 2.5 mg/kg bodyweight, with the lower dose of 0.5 mg/kg bodyweight being non-significant. No studies using LPS models have shown a reduction in Ilb, Il10 or Il6 expression (Table 1), implying differences in molecular outcomes between LPS and poly(I:C) models. Of particular note, only Il6, Il1b and Tnfa have all been analysed in the fetal brain in both rat and mouse LPS and poly(I:C) models. These results are shown in Fig. 6, which demonstrates the temporal changes in expression between model types. This critically indicates the disparity in outcome measures between both rodent species and immunogen. Further, conflicting results for expression of these cytokines within a model can frequently be attributed to immunogen dosage, gestational timing of immune induction or whether RNA or protein expression was analysed.

3.4.2. Neurotransmission/neuronal signalling gene expression in mIA-exposed offspring brain tissues

The second largest functional group of genes (n = 27), were involved in neural signalling pathways (Table 2), and could be subgrouped into five categories: GABAergic signalling (Gad1, Gad2, Gabra 1-5, Slc12a2, Slc12a5, Oxt), glutamatergic signalling (Slc1a1-3, Slc17a7, Grin1, Grin2a, Grin2b), dopaminergic signalling (Drd1, Drd2, Comt, Th, Slc6a3), neuregulin signalling (Nrg1, ErbB4) and neurotrophic signalling (Bdnf, Ngf, Ntrk2).

Within the GABAergic subgroup, the enzymes GAD65 and GAD67 are the most extensively studied. These enzymes are encoded by the Gad2 and Gad1 genes, respectively, and synthesize GABA from glutamate. The majority of studies that analysed one or both of these genes
Table 3
Neurodevelopmental gene expression changes in mIA offspring relative to controls.

| GENE (PROTEIN) | TISSUE | AGE | OUTCOME | MODEL | REFERENCES |
|---------------|--------|-----|---------|-------|------------|
|               |        |     | Protein / RNA |       |            |
| Akt1 (AKT1)   | PFC    | A   | ↑  | M-PIC | Willi et al., 2013RM |
|               | Striatum | A | N  | M-PIC | Willi et al., 2013RM |
| Whole brain   | F      | N  | /↑  | R-LPS | Ginsberg et al., 2018RM |
| Middle brain  | P / A  | N  | /↑  | M-INF | Fatemi et al., 2005RM |
| Nos1 (nNOS)   | Rostral brain | P / A | 1↑ / 1↑ | M-INF | Fatemi et al., 2004RM |
|               | Caudal brain | PA | N  | M-INF | Fatemi et al., 2004RM |
|               | Nuncian | P  | M-INF | Fatemi et al., 1998RM |
|               | Disc1 (DISC1) | J / PA | 1↑ / N  | R-PIC | Duchatel et al., 2019RM |
| Rln (Reelin)  | CB      | N  | M-PIC | O’Loughlin et al., 2017RM |
|               | Cere Cortex | A | N  | M-PIC | Enshili et al., 2020P |
| F Cortex      | J      | N  | M-PIC | Enshili et al., 2020P |
| Amygdala      | J / P  | N  | /↑  | M-PIC | O’Loughlin et al., 2017RM |
|               | Striatum | P  | 1↑  | M-PIC | Enshili et al., 2020P |
|               | C Callorum | P  | 1↑  | M-PIC | Enshili et al., 2020P |
|               | Fimbria  | P  | N  | M-PIC | Enshili et al., 2020P |
| Ventricile    | P      | N  | M-PIC | Enshili et al., 2020P |
| Hipp          | J      | R  | R-PIC | Chamara et al., 2020RM |
| Whole brain   | F      | N  | M-PIC | Zhao et al., 2019RM |
|               |        |     |       |       | R-PIC: Enshili et al., 2020P |
|               |        |     |       |       | (continued on next page)
Table 3 (continued)

| GENE (PROTEIN) | TISSUE | AGE | OUTCOME | MODEL | INDUCTION TIME | REFERENCES |
|----------------|--------|-----|---------|-------|----------------|------------|
| Cdo8 (CDDO)   | Whole brain | F | ↑ Np | M-PIC | E – early-mid; L – late | Nakamura et al., 2019<sup>MP</sup> |
|                | Hipp    | J | N<sup>R</sup> | R-PIC | Females only analysed | Chamera et al., 2020<sup>R</sup> |
|                | Plp1    | J | N<sup>R</sup> | R-PIC | Females only analysed | Zhao et al., 2019<sup>R</sup> |
|                | F Ctx   | J | N<sup>P</sup> | R-PIC | Females only analysed | Chamera et al., 2020<sup>R</sup> |
|                | Whole brain | F | ↑ Np | M-PIC | Females only analysed | Nakamura et al., 2019<sup>MP</sup> |
|                | Hipp    | J | J<sup>RM</sup> | R-PIC | Females only analysed | Nakamura et al., 2019<sup>MP</sup> |
| Bcl1 (IBA1)   | Hipp    | N | N<sup>R</sup> | M-PIC | Females only analysed | Chamera et al., 2020<sup>MP</sup> |
|                | F Cortex | J / A | N<sup>R</sup> / ↑ N<sup>R</sup> | M-PIC | Females only analysed | M-PIC: Mattei et al., 2014<sup>MP</sup> |
|                | Motor cortex | NA | N<sup>P</sup> | M-PIC | Females only analysed | Ratnayake et al., 2012<sup>MP</sup> |
|                | CB      | N | N<sup>R</sup> | M-PIC | Females only analysed | Ratnayake et al., 2012<sup>MP</sup> |
|                | Whole brain | N / JPA | ↑ N<sup>R</sup> / ↓ N<sup>R</sup> | M-PIC | Females only analysed | Ratnayake et al., 2012<sup>MP</sup> |
|                | Hipp    | J | N<sup>R</sup> | M-PIC | Females only analysed | Ratnayake et al., 2012<sup>MP</sup> |
| Gfap (GFAP)   | Hipp    | N | N<sup>R</sup> | M-PIC | Females only analysed | Mattei et al., 2011<sup>MP</sup> |
|                | F Cortex | J / A | N<sup>R</sup> / ↑ N<sup>R</sup> | M-PIC | Females only analysed | Fatemi et al., 2004<sup>MP</sup> |
|                | Motor cortex | NA | N<sup>P</sup> | M-PIC | Females only analysed | Fatemi et al., 2005<sup>MP</sup> |
|                | CB      | N | N<sup>P</sup> | M-PIC | Females only analysed | Fatemi et al., 2006<sup>MP</sup> |
|                | Whole brain | N | N<sup>P</sup> | M-PIC | Females only analysed | Fatemi et al., 2006<sup>MP</sup> |
|                | Hipp    | P | N<sup>P</sup> | M-PIC | Females only analysed | Fatemi et al., 2006<sup>MP</sup> |
| Mbp (MBP)     | CB      | N / JP / A | N<sup>R</sup> / ↑ N<sup>R</sup> / ↓ N<sup>P</sup> | M-INF | Females only analysed | Mattei et al., 2009<sup>MP</sup> |
|                | A       | N<sup>R</sup> | M-INF | Females only analysed | Mattei et al., 2009<sup>MP</sup> |
|                | Nac     | A | N<sup>P</sup> | M-PIC | Females only analysed | Richetto et al., 2017<sup>MP</sup> |
|                | Pfc     | A | N<sup>P</sup> | M-PIC | Females only analysed | Richetto et al., 2017<sup>MP</sup> |
|                | Cere Cortex | JA | N<sup>R</sup> | M-PIC | Females only analysed | Nakamukodo et al., 2008<sup>MP</sup> |
|                | Hipp    | N / JP | ↑ N<sup>P</sup> / ↓ N<sup>P</sup> | M-INF | Females only analysed | Fatemi et al., 2009<sup>MP</sup> |
|                | CB      | N / JP / A | ↑ N<sup>R</sup> / N<sup>P</sup> / N<sup>N</sup> / N<sup>P</sup> | M-INF | Females only analysed | Fatemi et al., 2009<sup>MP</sup> |
| Neg (MAG)     | Hipp    | N / JPA | ↑ N<sup>P</sup> / ↓ N<sup>P</sup> | M-INF | Females only analysed | Fatemi et al., 2009<sup>MP</sup> |
|                | PFC     | A | N<sup>P</sup> | M-PIC | Females only analysed | Richetto et al., 2017<sup>MP</sup> |
| Neg (MAG)     | NAC     | A | N<sup>P</sup> | M-PIC | Females only analysed | Richetto et al., 2017<sup>MP</sup> |
|                | Amygdala | A | N<sup>P</sup> | M-PIC | Females only analysed | Zhang et al., 2020<sup>MP</sup> |
|                | NAc     | A | N<sup>P</sup> | M-PIC | Females only analysed | Zhang et al., 2020<sup>MP</sup> |
|                | Thalamus | A | N<sup>P</sup> | M-PIC | Females only analysed | Zhang et al., 2020<sup>MP</sup> |
| Neg (MAG)     | Hipp    | N / JPA | ↑ N<sup>P</sup> / ↓ N<sup>P</sup> | M-INF | Females only analysed | Fatemi et al., 2009<sup>MP</sup> |
| Mbp (MBP)     | CB      | NJP | N<sup>P</sup> / ↑ N<sup>P</sup> / ↓ N<sup>P</sup> | M-INF | Females only analysed | Fatemi et al., 2009<sup>MP</sup> |
|                | PFC     | A | N<sup>P</sup> | M-PIC | Females only analysed | Richetto et al., 2017<sup>MP</sup> |
| Mbp (MBP)     | Nac     | A | N<sup>P</sup> | M-PIC | Females only analysed | Richetto et al., 2017<sup>MP</sup> |
|                | Hipp    | N / JPA | ↑ N<sup>P</sup> / ↓ N<sup>P</sup> | M-INF | Females only analysed | Fatemi et al., 2009<sup>MP</sup> |
| Mohp (MOBP)   | CB      | NJ / PA | N<sup>P</sup> / ↑ N<sup>P</sup> | M-INF | Females only analysed | Fatemi et al., 2009<sup>MP</sup> |
|                | PFC     | A | N<sup>P</sup> | M-PIC | Females only analysed | Richetto et al., 2017<sup>MP</sup> |
| Mog (MOG)     | Hipp    | N / JPA | N<sup>P</sup> / ↓ N<sup>P</sup> | M-INF | Females only analysed | Fatemi et al., 2009<sup>MP</sup> |
| Plp1 (PLP)    | Hipp    | N / J / PA | N<sup>P</sup> / ↑ N<sup>P</sup> / N<sup>R</sup> / N<sup>P</sup> / ↑ N<sup>P</sup> | M-INF | Females only analysed | Fatemi et al., 2009<sup>MP</sup> |

Compiled neurotransmission gene expression changes in mIA models. Within a row forward slashes have been used to separate different outcome data within the same tissue at different timings and/or within different methodologies, and align across the row in each column. Where the same tissue/timepoint has been indicated only for analyses in tissues where outcome measures share a relationship with timing of gestational induction.

MODEL abbreviations: M-PIC – mouse-poly(IC); R-PIC – rat-poly(IC); M-LPS – mouse-LPS; R-LPS – rat-LPS. Gestational timing of immune induction time for mIA models has been indicated only for analyses in tissues where outcome measures share a relationship with timing of gestational induction.
have shown no significant changes in expression in fetal, neonatal and juvenile timepoints at any tissue assessed. By comparison, in adolescent and adult tissue, several significant changes have been identified for both genes in tissue- and age-dependent patterns (Table 2). Of note, in the PFC, there is a developmental change in expression of these two genes, with all studies showing no changes in mIA-affected juvenile offspring and a decrease in mIA-affected offspring in adulthood (Cassella et al., 2016; Labouesse et al., 2015a; Richetto et al., 2014). One study demonstrated no change in adulthood (Dickerson et al., 2014). By comparison, Gad2 and Gad1 have been shown to be unchanged in the adult striatum, cerebellum, cerebral cortex, and the frontal, piriform and parietal cortices (Cassella et al., 2016; Duchatel et al., 2019; Fatemi et al., 2017; Tang et al., 2013). Only Gad1 was analysed in the hippocampus, with both significant and non-significant expression changes identified (Cassella et al., 2016; Dickerson et al., 2014; Tang et al., 2013). In part, this divergence appears dependent on hippocampal region and timing of gestational immune induction. By contrast, the ionotropic GABA receptor subunits, of the GABA_A family, have shown prevalent non-significant changes across all tissues and timepoints analysed, although with no overlap between studies (Table 2). Adult PFC was the only tissue with significant changes of multiple receptor subunits, where subunit expression changes were as follows: Gabra1, non-significant; Gabra3, increased; Gabra2, 4 and 5, decreased (Richetto et al., 2014, 2015). The final three genes were the oxytocin receptor, Oxtr, and ion channels, Slc12a2 and Slc12a5, proposed to be involved in the GABA excitatory-to-inhibitory shift (Ben-Ari et al., 2012; Leonzino et al., 2016). Results showed developmental fluctuations in expression for Slc12a2 and Slc12a5 (Corradini et al., 2018; Richetto et al., 2014) and no changes of Oxtr (Morais et al., 2018; Ronovsky et al., 2017).

The glutamatergic subgroup included three glutamate re-uptake transporters (Slc1a1-3), assessed by only two studies, and the vesicular glutamate transporter (Slc17a7), with predominantly non-significant results (Kentner et al., 2016; McColl and Piquette-Miller, 2019; Tang et al., 2013). However, when significant changes were identified, the glutamate re-uptake transporter genes were exclusively decreased in expression: Slc1a3 in the fetal whole brain, Slc1a2 in the adult PFC and Slc1a3 in the adult hippocampus, while Slc17a7 was decreased in the cortex and increased in the hippocampus. The remaining genes within the glutamatergic signalling group were three glutamate ionotropic receptor subunits: Grin1, Grin2a and Grin2b, which appear to show developmental patterns of expression, with reduction in expression in mIA-affected offspring at juvenile time-points followed by increases in adulthood. Analysis of these genes has been repeated by more than one study in the adult PFC and hippocampus, and the results appear to vary with model type and gestational timing of immune induction (Fig. 7).

In contrast to GABAergic and glutamatergic subgroups, the majority of genes analysed within the dopaminergic subgroup were non-significant in every tissue and timepoint analysed. Three of the genes within this subgroup are associated with dopamine availability: Comt (catechol-O-methyltransferase) an enzyme which functions in the degradation of dopamine, Slc6a3 (dopamine transporter), which actively transports dopamine out of the synaptic cleft, and Th (tyrosine hydroxylase) which synthesises dopamine from tyrosine. These three genes in particular show few changes. Indeed, Comt showed no changes in all analyses, while Slc6a3 showed only significant decreases and only in one study (Vuillermot et al., 2010) where it was decreased in the fetal/adolescent nucleus accumbens (NAc) and adolescent caudate putamen (CPu). By contrast, Th has been investigated in more studies, but where a tissue has been analysed by more than one study, results have typically diverged by methodology with the most prevalent finding being non-significant changes in expression. Dopamine receptors 1 (Drd1) and 2 (Drd2), have been analysed in a total of nine tissues and have been shown to exhibit no significant changes in mIA-offspring in the ventral tegmental area (VTA), olfactory bulb, striatum, substantia nigra (SN), and CPu, the latter three of which have been replicated at adult timepoints. Notably, in the fetal whole brain, expression of both dopamine receptor genes has been shown to be significantly altered in mIA-offspring, however outcome for both genes appears heavily dependent on methodology (Fig. 7).

The remaining two subgroups were those involved in neurotrophic and neuregulin signalling. However, while these groups have been extensively investigated, there is limited reproducibility and often, as with immune genes, disparity in results is due to methodological heterogeneity. Two genes in the neuregulin signalling pathway indentified were the Erbb4 receptor and ligand Nrg1. In the fetal whole brain, Nrg1 and Erbb4 expression was influenced by gestational timing of mIA induction, with increases following late-induction but no change following early-mid induction in both rat-LPS and mouse-poly(I:C) models (Dabbah-Assadi et al., 2019). In postnatal tissue, Erbb4 expression was unchanged in the adolescent and adult hippocampus and PFC (Fatemi et al., 2008a; Hemmerle et al., 2015). Similarly, Nrg1 was unchanged in nearly all postnatal tissues, aside from a significant reduction
3.4.4. Neurodevelopmental gene expression changes in mIA offspring brain tissues

The smallest functional group of genes were those associated with neurodevelopmental processes (n = 26), however it should be noted that genes grouped into the other two classifications are also inherently critical in normal brain development. The 26 genes (Table 3) are involved in a range of neurodevelopmental processes and can be subdivided into: NDD risk factor genes (Auts2, Reln, Disc1), enzymes (Nos1, Nos2, Akt1), neuro patterning proteins (Foxp2, Dlx1, Shh, Fgf8), nuclear receptors (Nr4a2, Nr2f1), synaptic proteins (Syp, Snap25,Dlg4), interneuron markers (Pvlih, Sst) and those involved in glial cell development and function (Iba1, C668, Gfap, Mbp, Mag, Mog, Mal, Plp1, Mobb). Surprisingly, despite the underpinning hypothesis that mIA-derived offspring functional deficits arise due to neurodevelopmental perturbations, most of the genes in this functional clustering had limited inter-study overlap in analyses. In particular, within each tissue and developmental time point, Nos1, Nr4a2, Dlx1, Foxp2, Snap25, C668, Mal, Mobb, Mog, Plp1 and all three NDD risk factor genes (Disc1, Reln, Auts2) have no expression data extracted from more than one study. Further, Reln has shown no significant changes in expression across studies to date.

Two enzymes that had within-tissue overlaps in analysis were Akt1 serine-threonine kinase, involved in several brain developmental processes, and Nos2, inducible nitric oxide (NO) synthase, important in the synthesis of the cellular signalling molecule, NO. Akt1 was decreased in the adult PFC (Bitanahirew et al., 2010; Willi et al., 2013) and Nos2 increased in the adolescent hippocampus (Eshhilli et al., 2020; Zhao et al., 2019). Of note, while having no other incidences of inter-study analysis overlaps, when expression of Nos1 or Nos2 has been identified as significantly altered in mIA-affected offspring, there has been a unilaterial increase relative to control offspring (Table 3). By comparison, for the neuro-patterning protein and nuclear receptor groups, all replicated results were mostly non-significant: Fgfl growth factor, had no change in expression in a rat-poly(I:C) model but did demonstrate a significant increase in expression in a mouse-poly(I:C) model 2d post-induction while Shh, a developmental morphogen, was non-significant in both (Meyer et al., 2008a; Okawara et al., 2015) and Nr2f1, a steroid hormone receptor, was replicated as having unaltered expression in the adult hippocampus (Fatemi et al., 2012; Tang et al., 2013).

Results for synaptic proteins and interneuron markers were more variable, with the exception of Pvalb, encoding parvalbumin, a calcium binding protein enriched in a subset of GABAergic interneurons, which was unchanged in every tissue analysed, a result which was replicated in the adult cerebral cortex (Duchatet et al., 2019; Rahman et al., 2020). Results for the reming circuits in these two subgroups were often dependent, in part, on methodology. For example, Sst, encoding the growth hormone inhibitor somatostatin, also enriched in a subset of interneurons, was replicated as decreased in mIA-affected offspring in the adult cerebral cortex following late gestational immune induction in two rat-poly(I:C) models (Duchatet et al., 2019; Rahman et al., 2020) but opposing results were found in the same two studies following early
gestational immune induction with both unchanged (Duchatel et al., 2019) and decreased expression observed (Rahman et al., 2020). By comparison, expression of Syt, a major synaptic vesicle protein, was unaltered in the adult hippocampus in mouse-poly(I:C) models following both early-mid gestational immune induction at a dose of 20 mg/kg bodyweight and late gestational immune induction at a dose of 5 mg/kg bodyweight (Giovanoli et al., 2015; Ibi et al., 2020), but was increased following early-mid gestational immune induction at a dose of 8 mg/kg bodyweight (Giovanoli et al., 2016). Meanwhile, expression of Dlk4, a guanylate kinase localised to the synaptic membrane, was decreased in the adolescent and adult hippocampus in a mouse-poly(I:C) model but non-significant and increased, respectively, in a rat-poly(I:C) model (Giovanoli et al., 2016; Hao et al., 2019). Notably Dlk4 results display clear heterogeneity across tissues and developmental time points with several instances of no changes, increases and decreases in expression in mIA-affected offspring (Table 3).

Finally, by far the largest subgroup of genes within the neuro-developmental gene cluster included genes involved in normal glial development and functions. As stated, Cd68, a glycoprotein localised to the microglial membrane, has no analysis performed between multiple studies in any tissue or time point. However, a secondary, calcium-binding protein enriched at the microglial membrane, Iba1, has been far more extensively analysed. Notably, in the hippocampus, studies have shown decreased expression in mIA-affected offspring from neonatal through to adult time points (Chamara et al., 2020; Mattei et al., 2014; Ratnayake et al., 2012). Further, in the adult hippocampus and cerebellum where more than one study has provided analysis, results were methodology-dependent. In the adult cerebellum there were no changes in expression in a mouse-poly(I:C) model but decreased expression in a rat-poly(I:C) model (Mattie et al., 2014), while in the adult hippocampus no changes were seen in a mouse-poly(I:C) model (Ratnayake et al., 2012) while two rat-poly(I:C) models, both using a mid-late gestational immune induction at 4 mg/kg bodyweight, have directly opposed each other with one showing no changes in expression in mIA-affected offspring and one showing decreased expression (Chamara et al., 2020; Mattei et al., 2014). By comparison, Gfap, an astrocyte-specific protein, important in astrocyte specification, reactive astrogliosis and formation of the blood brain barrier, exhibited no changes in expression across multiple tissues and time-points, with this data replicated extensively in the neonatal and adolescent hippocampus (Ding et al., 2019; Fatemi et al., 2009b; Kirsten et al., 2012; Ratnayake et al., 2012). Indeed, only Fatemi and colleagues, using an mouse-influenza model, and Ding and colleagues using a rat-poly(I:C) model, have identified significant changes in Gfap expression in mIA offspring, with increased expression in the neonatal whole brain (Fatemi et al., 2004, 2005) and then decreased (Fatemi et al., 2009b) or increased (Ding et al., 2019) expression in the adult hippocampus. The remaining genes in this subgroup were those involved in myelination and, as highlighted, the majority have shown no replication between studies (Fatemi et al., 2005, 2009a, 2009b; Richetto et al., 2017a). However, when a significant effect was identified for these genes they were primarily significant decreases in expression in mIA-affected offspring, with the only significant increases seen in mouse-influenza models for Mbp in the adult hippocampus (Fatemi et al., 2009b) and Plp1 in the juvenile hippocampus and adolescent and adult cerebellum (Fatemi et al., 2009a). Within the myelination group, Mbp and Mag were the only genes that have been analysed by more than one study in a given tissue. Results for Mb p have been replicated as non-significantly altered in the adult hippocampus (Fatemi et al., 2009b; Makinodan et al., 2008) while in the juvenile hippocampus, results were disparate between mIA-model types, with a significant decrease in expression in a mouse-poly(I:C) model (Makinodan et al., 2008) and no change in an mouse-influenza model (Fatemi et al., 2009b). By comparison, Mag expression was replicated as decreased in the adult PFC (Richetto et al., 2017a; Zhang et al., 2020) while in the adult hippocampus, expression was decreased in a mouse-poly(I:C) model (Zhang et al., 2020) and increased in an mouse-influenza model (Fatemi et al., 2009b).

3.5. Global gene expression analyses in mIA models

While candidate gene studies are critical for validation of changes in gene expression, such work is inherently biased towards our current mechanistic understanding and associated hypotheses of the molecular pathways that underpin disease phenotypes. It is therefore critical that non-candidate studies are conducted in an effort to identify novel pathways not based on previous hypotheses. Multiple studies included in our review have adopted this approach to analyse gene expression changes. However, it is evident that results from such studies vary greatly in the identification of significantly affected genes. Indeed, while a considerable number of non-candidate driven studies have shown differential expression in a number of genes, the total numbers fluctuate from tens of genes to thousands. Additionally, a number of studies have demonstrated no significant changes in gene expression when using these techniques. Table 4 summarises the results from global gene expression analyses. The results have been categorised by immunogen used, species, gestational timing of immune induction, offspring age and tissue type analysed and summarise whether significant results were found and, where significant changes were identified, the number of genes up or downregulated. Full data can be found in Supplement 2. It is worth noting that the capacity of each method for analysing gene expression will inherently limit the number of identified genes; for example, RNA-seq will be able to capture more genes than microarrays. However, it is evident from the studies included in the review that the number of differentially expressed genes varies even across microarray studies (Table 4). Results are also disparate between offspring age, tissue and gestational timing of immune induction, highlighting how different methodologies directly impact on biological outcomes.

Next we considered whether any of the 88 candidate genes were identified in global gene expression analyses. A total of 21, 17 and 21 of the candidate genes across immune/stress response, neurotransmission/neuronal signalling and neurodevelopmental groups, respectively, were identified in at least one study using global gene expression analysis (Table 5). However, there were few cases where studies using candidate and global analysis had analysed the same tissue or developmental time point and, where they had, this was within the same study. Nonetheless, where direct comparison was possible within a given tissue/time point, we determined if expression data for these candidate genes was replicated between the two study approaches. We have identified several genes for which both approaches have established the same outcome measurement for directionality of expression. However, it is evident that methodological differences influence the comparability between studies. In addition, there are multiple instances where significant changes in expression were identified in global gene expression analysis in a tissue or time-point not yet analysed by candidate approaches and thus these studies have expanded on the results obtained by currently published candidate gene analysis outlined in Tables 1–3. For candidate genes within the immune/stress response group, significant changes identified via global gene expression analysis were highly diverse, and dependent on methodology, as described for candidate-driven gene studies (Tables 1 and 5), while in the neurodevelopmental gene group, additional results were identified in global gene expression analysis, for all but Dlx1, Shh and Plp1. Notably, Rehn was shown to be decreased in expression in the adult amygdala in global gene expression analysis (Weber-Stadlbauer et al., 2017) while all candidate-driven approaches have shown no changes in expression of Rehn (Table 2). Further, for the myelination genes that showed significant changes in expression in global gene expression analysis, these results frequently supported those identified in candidate-driven studies, with an overall decrease in expression in mIA-affected offspring. By comparison, within the neurotransmission group, expression of GABA_A receptor subunits 1–5 were all significantly altered in fetal whole brain and several prenatal tissues in global gene expression approaches, while they were
of the critical pathways identified by candidate studies, we also evaluated GO for biological processes for all genes showing differential expression in at least one non-candidate study (Supplement 6). 764

Results are shown by model type and gestational induction if mIA. Tissue type and age are shown alongside results. Tissue Abbreviations: Hipp - Hippocampus; PFC – Prefrontal Cortex; CB – Cerebellum; GD - gestational day; P - postnatal day; wk - week. Study Abbreviations: *validated mIA; M – males only analysed.

mostly unchanged in expression in candidate-driven studies.

Identification of multiple candidate genes as differentially expressed in at least one global study supports their importance in the underlying biological processes, emphasising the importance of non-candidate studies for
| GENES (PROTEIN) | GROUP | CHANGES IDENTIFIED | MODEL | CHANGES IDENTIFIED | RESULTS REPLICATED BETWEEN APPROACHES | REFERENCES |
|----------------|-------|--------------------|-------|--------------------|----------------------------------------|------------|
| Arg1* (ARG-1) | 1     | ↑ F WB | M-PIC | ↑ F WB | M-PIC | Y | Tuivion-Visbord et al., 2020; Money et al., 2018 |
| Arg4* (AQP-4) | 1     | ↑ N Hipp | M-INF | ↑ N Hipp | M-INF | Y | Fatemi et al., 2009a, 2005 |
| Cap3 (CASP-3) | 1     | ↑ F WB | M-PIC | ↑ F WB | M-PIC | Y | Tsivion-Visbord et al., 2020 |
| Ccl2 (MCP-1)  | 1     | NS J Cortex | M-PIC | - | - | - | Tang et al., 2013 |
| Cxcl1* (CXCL1) | 1 | ↑ | M-PIC | - | - | - | Tsivion-Visbord et al., 2020 |
| Fkbp5* (FKBP5) | 1 | ↑ F WB | R-LPS | ↑ F WB | R-LPS | Y | Oskvig et al., 2012; Ginsberg et al., 2018 |
| Cxcl10 (IP-10) | 1 | ↑ F WB | M-PIC | NS F WB | M-PIC | N | Tsivion-Visbord et al., 2020; Arrode-Brus et al., 2012 |
| Cxcl12 (GM-CSF) | 1 | ↑ F WB | M-PIC | ↑ F WB | M-PIC | Y | Tsivion-Visbord et al., 2020; Openshaw et al., 2019; Arrode-Brus et al., 2012 |
| Il1b (IL-1β) | 1 | NS J Cortex | M-PIC | - | - | - | Tang et al., 2013 |
| Il10 (IL-10)  | 1 | NS J Cortex | M-PIC | - | - | - | Tang et al., 2013 |
| Il18* (IL-18) | 1 | ↑ | M-INF | ↑ | M-INF | - | Fatemi et al., 2008a |
| Ccl2 (MIP-1α) | 1 | ↑ F WB | M-PIC | ↑ F WB | M-PIC | Y | Tuivion-Visbord et al., 2020; Simões et al., 2018; Garcia-Vaillan et al., 2020 |
| Mmp9 (MMP-9) | 1 | ↑ F WB | M-PIC | ↑ F WB | M-PIC | Y | Garbett et al., 2012; Simões et al., 2018; Arrode-Brus et al., 2012 |
| Nr3c1 (GCR)  | 1 | NS J Cortex | M-PIC | - | - | - | Weber-Stadlbauer et al., 2017 |
| Nfkb1 (NF-κB) | 1 | ↑ F WB | R-LPS | ↑ F WB | R-LPS | Y | Tsivion-Visbord et al., 2020; Núñez-Estevez et al., 2020 |
| Npy* (NPY)  | 1 | ↑ F WB | M-PIC | ↑ F WB | M-PIC | Y | Fatemi et al., 2009a |
| Nrc2 (RANTES) | 1 | ↑ F WB | M-PIC | ↑ F WB | M-PIC | Y / N | Tuivion-Visbord et al., 2020; Openshaw et al., 2019; Arrode-Brus et al., 2012 |
| Pigs2* (COX-2) | 1 | A PFC, P CB | M-INF | ↑ | M-INF | - | Fatemi et al., 2008a, 2008b |
| Tnfa (TNFα) | 1 | ↑ F WB | M-PIC | ↑ F WB | M-PIC | Y / N | Tuivion-Visbord et al., 2020; O’Loughlin et al., 2017 |
| Gad1* (GAD67) | 2 | ↑ F WB | R-LPS | ↑ F WB | R-LPS | Y / N | Tang et al., 2013 |
| Gad2* (GAD65) | 2 | ↑ F WB | R-LPS | ↑ F WB | R-LPS | Y / N | Tsivion-Visbord et al., 2020; Openshaw et al., 2019; Arrode-Brus et al., 2012 |
| Gabra1* (GABAAR<sub>1</sub>) | 2 | ↑ F WB | M-INF | ↑ F WB | M-INF | Y | Tsivion-Visbord et al., 2020 |
| Gabra2* (GABAAR<sub>2</sub>) | 2 | ↑ F WB | M-INF | ↑ F WB | M-INF | Y | Fatemi et al., 2008a, 2009b |
| Gabra3* (GABAAR<sub>3</sub>) | 2 | ↑ F WB | M-INF | ↑ F WB | M-INF | Y | Fatemi et al., 2014, 2015, 2017a |
| Gabra4* (GABAAR<sub>4</sub>) | 2 | ↑ F WB | M-INF | ↑ F WB | M-INF | Y | Oskvig et al., 2012; Tuivion-Visbord et al., 2020 |
| Gabra5* (GABAAR<sub>5</sub>) | 2 | ↑ A CB | M-INF | ↑ A CB | M-INF | Y | Oskvig et al., 2012; Weber-Stadlbauer et al., 2017 |
| Grin2a* (NR2A) | 2 | ↑ J WB, A NAc | M-INF | ↑ J WB, A NAc | M-INF | Y | Fatemi et al., 2008a, 2009a, 2017 |
| Grin2b* (NR2B) | 2 | ↑ J WB, A NAc | M-INF | ↑ J WB, A NAc | M-INF | Y | Sunwoo et al., 2018; Richetto et al., 2017a |

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### Table 5 (continued)

| GENE (PROTEIN) | GROUP | CHANGES IDENTIFIED | MODEL | NON-CANDIDATE RESULTS | COMPARABLE CANDIDATE RESULTS | MODEL | RESULTS REPLICATED BETWEEN APPROACHES | REFERENCES |
|----------------|-------|-------------------|-------|-----------------------|-----------------------------|-------|---------------------------------------|------------|
| **Grin2B** (NR2B) | 2     | † A Amygdala      | M-PIC | † F WB                | M-PIC                        |       | Y / yes; N / No                       |            |
| **Drd1** (D1R) | 2     | † A Amygdala      | M-PIC | † A PFC               | N A PFC                      | M-PIC | N                                     |            |
| **Drd2** (D2R) | 2     | † A Amygdala      | M-PIC | † F WB / NS F WB      | M-PIC / R-LPS                |       | Y / N                                 |            |
| **Slc6a3** (DAT) | 2     | † A Amygdala      | M-PIC |                       |                             |       |                                       |            |
| **Th** (TH) | 2     | † P CB            | M-INF |                       |                             |       |                                       |            |
| **Slc1a2** (EAAT2) | 2     | † F WB            | M-PIC | NS F WB               | R-PIC                        |       | N                                     |            |
| **Nrx1** (NRR1) | 2     | † P CB; † N Hipp  | M-INF |                       |                             |       |                                       |            |
| **Nr2f1** (NR2F1) | 3     | NS J Cortex       | M-PIC |                       |                             |       |                                       |            |
| **Dlx1** (DLX1) | 3     | † F WB            | R-LPS | † F WB                | R-LPS                        |       | Y                                     |            |
| **Dlx2** (LSM2) | 3     | † N Hipp          | M-INF |                       |                             |       |                                       |            |
| **Dlx3** (LSM2) | 3     | † N Hipp          | M-INF |                       |                             |       |                                       |            |
| **Dlx4** (FOXP2) | 3     | † N Hipp          | M-INF |                       |                             |       |                                       |            |
| **Shh** (SHH) | 3     | † F WB            | M-INF |                       |                             |       |                                       |            |
| **Prab1** (Parvalbumin) | 3     | † P Neocortex     | M-INF |                       |                             |       |                                       |            |
| **Snr** (SST) | 3     | † J WB            | M-PIC |                       |                             |       |                                       |            |
| **Iba1** (IBA1) | 3     | † J CB            | M-INF |                       |                             |       |                                       |            |
| **Gfap** (GFAP) | 3     | † J CB            | M-INF |                       |                             |       |                                       |            |
| **Mbp** (MBP) | 3     | † F WB            | M-PIC |                       |                             |       |                                       |            |
| **Mag** (MAG) | 3     | † J CB            | M-INF |                       |                             |       |                                       |            |
| **Mal** (MAL) | 3     | † J CB; † A CB    | M-INF | NS J CB / † A CB      | M-INF                        |       | N / Y                                 |            |
| **Md5p** (MOBP) | 3     | † J CB; † A CB    | M-INF |                       |                             |       |                                       |            |

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broadening our understanding of key pathways in NDD pathology.

3.6. Epigenetic markers in mIA models

Epigenetic mechanisms can broadly be divided into three key areas: DNA modifications, histone modifications and non-coding RNAs. All three mechanisms are known to regulate gene expression and are critical for cellular development and function (Kundaje et al., 2015; Quina et al., 2006). The increasing interest in understanding the role of epigenetic mechanisms in complex brain disorders is, in part, due to the importance of epigenetic mechanisms in normal brain development and function. Indeed, a number of monogenic disorders with perturbed brain function originate from mutations in genes critical for normal epigenetic regulation (Jakovcevski and Akbarian, 2012). Furthermore, rather uniquely, mature neurons lack mitotic activity and do not maintain stringent regulation of epigenetic markers. Hence, neurons may be more affected by epigenetic dysfunction than other cells (Christopher et al., 2017).

In the context of mIA, epigenetic mechanisms are critically important as they are hypothesised to be the mediators by which mIA promotes the pathogenesis of NDDs. It has been demonstrated that epigenetic patterns respond to environmental triggers and are programmable from the fetal environment. Therefore, altered epigenetic mechanisms could predispose offspring to NDDs following insults to normal brain development (Millan et al., 2013); however, few studies in mIA models have been conducted to date. Of those studies identified within the scope of this review (Table 6), all have been conducted in mouse-poly(I:C) models. Moreover, methodologies for analysing changes to epigenetic patterns are heterogeneous and use both candidate and non-candidate approaches across all the three key epigenetic mechanisms (Table 6). To date, no studies employing epigenetic analysis in mIA models have generated data for the same mechanism in the same tissue or developmental time point and hence direct comparison between studies could not be achieved. Nonetheless, initial studies investigating epigenetic mechanisms have yielded valuable insights, suggesting more changes with respect to DNA methylation than histone modifications in response to mIA with histone modifications showing non-significant changes (Connor et al., 2012; Reisinger et al., 2016; Tang et al., 2013), while several DNA methylation markers were found to be affected (Basí et al., 2018; Labouesse et al., 2015a; Richetto et al., 2017a, 2017b).

However, interestingly, candidate studies for DNA methylation and histone modifications have frequently correlated significant results with corresponding changes in expression of the targeted gene (Table 6). In addition, it is worth noting that of the 88 candidate genes analysed in more than one study, nine (Mog, Gad1, Gad2, Dbx1, Nr2F1, Nr4a2, Discl, Slc17a7, Tb) have been analysed for epigenetic alterations alongside changes in gene expression. Importantly, these studies provide preliminary evidence that changes in expression of these functional risk genes may result from disturbed epigenetic regulation. In future, we expect to see more publications exploring further epigenetic mechanisms that will allow a more comprehensive understanding of the role of epigenetic mechanisms as a regulatory framework involved in the aetiology of NDDs. Thorough investigation of this mechanistic framework is required to enhance our understanding of the molecular pathology underlying specific environmental risk factors, enabling the identification of molecular loci for new clinical interventions for NDDs.

4. Discussion

4.1. Gene expression changes in mIA models and implications for NDD research

Despite clinical demand and advances in the treatment of psychosis over the past 30 years, fully effective clinical management for NDDs is still difficult to achieve (Estes and McAllister, 2016; Meyer, 2019; Mullin et al., 2013; Murray et al., 2012; Thapar et al., 2017). Thus, significant research effort is focused on understanding the complex underlying aetiologies of these disorders. In the context of schizophrenia, mIA is proposed to underscore a distinct subgroup of patients (Clementz et al., 2016; Tammenga and Clementz, 2020), and understanding the mechanisms by which mIA alters neurodevelopmental trajectories and predisposes offspring to NDDs is critical for identifying therapeutic targets for these patients (Estes and McAllister, 2016; Meyer, 2019). To this end, the mIA model is an invaluable preclinical tool. Rodent models strive to replicate disease through construct, face and predictive validity (Fig. 8), and studies have begun to demonstrate the effectiveness of mIA models across these three areas and hence their suitability to model NDD pathophysiology (Meyer et al., 2016; Meyer and Feldon, 2010). Our systematic review therefore sought to contribute to the understanding of gene functional pathways that may underpin the aetiology of NDDs and be particularly relevant to our understanding of schizophrenia. Despite demonstrating that methodological approaches influence molecular results between studies, we were able to identify key genes and epigenetic markers showing significant changes in mIA-affected offspring. GO analysis for the 88 candidate genes analysed in more than one study (Supplement 4) highlighted three functional groups: immune/stress response, neurotransmission/neuronal signalling and neurodevelopment (Tables 1–3). Further, although candidate gene studies are inherently biased towards a priori hypotheses, many genes were also identified through non-candidate approaches (Table 5). Moreover, GO analysis for all non-candidate genes, which demonstrated differential expression in at least one global gene expression study (Supplement 6), showed that these genes were also enriched significantly for immune, neuronal signalling and neurodevelopmental processes, supporting the validity of candidate gene selections to date. Importantly, as these processes are hypothesised to be critical in the molecular pathology of NDDs, our results substantiate the molecular findings of mIA models to

![Table 5 (continued)](image-url)
| DNA methylation | Candidate | Study approach | Methods | Tissue | Epigenetic results | Corresponding gene expression | Study |
|-----------------|-----------|----------------|---------|-------|-------------------|-------------------------------|-------|
| Candidate | GD17, (i.p.) | MeDIP/ hMeDIP | P80-100 mPFC | Gad1 | 140% promoter methylation; 120% promoter hydroxymethylation | 20% Gad1 RNA | Labouesse et al., 2015M |
| Candidate | GD17, (i.v.) | EpiTYPER | −12wk PFC | Gad2 | 140% promoter methylation; NS promoter hydroxymethylation | 15% Gad2 RNA | Labouesse et al., 2015M |
| Candidate | GD9 OR GD17, (i.v.) | EpiTYPER | −P100 PFC | PFC, MOP (MOBP) promoter; † methylation at Cpg 507 & 457; † methylation at Cpg 343 | 30% RNA; NS Protein | Richetto et al., 2017M |

Histone modifications

| Candidate | GD9, (i.v.) | EpiTYPER | P90 Ventral Midbrain | AR42f (NURR1); no change in promoter methylation | AR42f NS RNA | NA |
| Candidate | GD12, (i.p.) | ChipP, H3/ H4ac | 8-12wk Hipp | † H3 and H4 acetylation at the Sert (SERT) promoter | SERT | 50% Protein | Reisinger et al., 2016M |
| Candidate | GD9, (i.p.) | ChipP-PCR: H4K8/ K9K14ac Promoter. | P24 Cortex | P24 Cortex Gria1 (GluR1): H4K8ac NS; † H4K9K14ac; P24 Cortex Robo1 (ROBO1): H4K8ac NS; † H4K9K14ac; P24 Cortex Arggpa8 (ARGGPA8): H4K8ac NS; † H4K9K14ac | H4K9K14ac | Arhgpa8 | 25% RNA |
| Candidate | GD9, (i.p.) | ChipP-PCR: H4K8/ K9K14ac Promoter. | P24 Hipp | P24 Hipp Nerk3 (TRK-C): H4K8ac NS; † H4K9K14ac | Nerk3 | 50% RNA |
| Candidate | GD9, (i.p.) | ChipP-PCR: H4K8/ K9K14ac Promoter. | P24 Hipp | P24 Hipp Gria1 (GluR1): H4K8ac NS; † H4K9K14ac | Gria1 | 75% RNA |
| Candidate | GD9, (i.p.) | ChipP-PCR: H4K8/ K9K14ac Promoter. | P24 Hipp | P24 Hipp Gria2 (GluR2): H4K8ac NS; † H4K9K14ac | Gria2 | 30% RNA |
| Candidate | GD9, (i.p.) | ChipP-PCR: H4K8/ K9K14ac Promoter. | P24 Hipp | P24 Hipp Nerk3 (TRK-C): H4K8ac NS; † H4K9K14ac | Nerk3 | 50% RNA |
| Candidate | GD9, (i.p.) | ChipP-PCR: H4K8/ K9K14ac Promoter. | P24 Hipp | P24 Hipp Dsc1 (DISCl): H4K8ac NS; † H4K9K14ac | Dsc1 | 160% RNA |
| Candidate | GD9, (i.p.) | ChipP-PCR: H4K8/ K9K14ac Promoter. | 3mo Cortex | 3mo Cortex Gria1 (GluR1): H4K8ac NS; † H4K9K14ac | Gria1 | 25% RNA |
| Candidate | GD9, (i.p.) | ChipP-PCR: H4K8/ K9K14ac Promoter. | 3mo Cortex | 3mo Cortex Robo1 (ROBO1): H4K8ac NS; † H4K9K14ac | Robo1 | 25% RNA |
| Candidate | GD9, (i.p.) | ChipP-PCR: H4K8/ K9K14ac Promoter. | 3mo Cortex | 3mo Cortex Slc17a7 (VGLUT1): H4K8ac NS; † H4K9K14ac | Slc17a7 | 30% RNA |
| Candidate | GD9, (i.p.) | ChipP-PCR: H4K8/ K9K14ac Promoter. | 3 mo Hipp | 3 mo Hipp: H4K8ac all non-significant. H4K9K14ac all non-significant. | No RNAA changes | NA |
| Candidate | GD9, (i.p.) | Western blot: global H3/ H4ac | 8-12wk Hipp | Global H4ac increased, Global H3ac decreased | NA | Reisinger et al., 2016A |
| Candidate | GD9, (i.p.) | Western blot: global H3/ H4ac | P24 Cortex | P24 cortex: H4K9K14ac; † H4K8ac | NA | Tang et al., 2013M |
| Candidate | GD9, (i.p.) | Western blot: global H3/ H4ac | P24 Hipp | P24 Hipp, 3mo Hipp, 3mo Cortex: H4K9K14ac NS, H4K8ac NS | NA | Tang et al., 2013M |
| Candidate | GD17, (i.v.) | ChipP-seq | 6wk Cortex | No significant changes identified | NA | Comparator et al., 2012 |
| Candidate | GD12, (i.p.) | RT-PCR | 8wk Hipp | miR-15b-2: (+25%); miR-96-1: (+20%); miR-103-2: (+10%); miR-124-1: (+25%); NS: miR-15a, miR-132-1, miR-212-3p-1, miR-212-5p-1, miR-16-2, miR-190-1, miR-144-3, miR-219-1, miR-219-2-3p-1 | NA | NA |
| Candidate | GD12, (i.p.) | miRNA microarray | 3wk Whole brain | 8 miRNAs which were upregulated and 21 miRNAs were downregulated | NA | Sunwoo et al., 2018M |

Epigenetic mechanisms and study approach have been indicated, followed by the study methodology including mA induction and epigenetic analyses. The table shows the tissue type analysed and results obtained. Abbreviations: PFC = Prefrontal Cortex, mPFC = Medial PFC, Hipp = Hippocampus, NAC = Nucleus Accumbens, Hypoth = Hypothalamus, V. Midbrain = Ventral Midbrain, NS = no significant changes, † significant increase, ‡ significant decrease, Ac = acetylation, wk = week, mo = month, *validated mA, M = males only analysed.
date and their relevance for studying disease mechanisms translational to human health.

4.1.1. Inflammation and stress responses

The immune/stress response group (Table 1) was predominantly comprised of cytokines and chemokines, extensively investigated in the fetal brain, with significant elevations and reductions throughout the 24 h period post-immune induction. *Il6*, *Il1b* and *Tnfa*, in particular, have been the most investigated candidate genes included in the review and, in the fetal brain, their expression patterns demonstrate clear delineations between model type (Fig. 6) with differences between both rodent species and immunogen used. The latter is not unexpected, as LPS (mimicking bacterial infection) and poly(I:C) (mimicking viral infection) elicit downstream signalling cascades via two different toll-like receptors (TLRs), TLR4 and TLR3, respectively. Therefore, this will promote different maternal cytokine profiles and, subsequently, divergent biological changes in the fetal brain. Cytokines are critical signalling molecules during neurodevelopment, involved in a broad range of processes from cell fate decisions to synaptic connectivity, and hence, temporal or regional disturbances in expression, as a result of maternal inflammatory triggers, are thought to be critical in mediating mIA outcomes (Ratnayake et al., 2013). Moreover, disturbances in immune/stress response gene expression in the mIA model persist into the postnatal brain (Table 1). This is of particular importance as we try to understand disease mechanisms underpinning NDD pathology. Chronic elevations of IL-6, IL-1β and TNFα have been associated with symptom severity in both autism and schizophrenia (Meyer, 2019; Ratnayake et al., 2014). Consistent with these findings in human patients, elevations in these cytokines were notable in several adult offspring brain tissues, though in regionally-specific patterns (Fig. 9), suggesting an altered adult brain neuroinflammatory profile of relevance to schizophrenia.

Taken together, data from both candidate (Table 1) and non-candidate approaches (Table 5), begin to validate the mIA model as sufficiently representative of inflammatory changes translational to human health. Of particular importance, these changes in inflammatory/stress markers may act as target pathways for therapeutic modulation. Indeed, review of anti-inflammatory agents and therapies to antipsychotics have shown promising alleviation of both positive and negative symptoms in schizophrenia spectrum disorders (Hong and Bang, 2020). Investigation of these candidates in the mIA model could therefore identify specific inflammatory pathways for further drug development. Additionally, profiling of blood inflammatory markers may have the potential to be used as biomarkers of pre-symptomatic disease progression or act to identify high-risk individuals, similar to those used to stratify treatment response in major depressive disorder (Mondelli et al., 2015).

4.1.2. Neurotransmission and neuronal signalling

Of the neuronal signalling pathways predominantly investigated within the mIA model, neurotransmitter pathways have received particular attention because of their important role in the pathophysiology of neurodevelopmental and neuropsychiatric disorders (Marotta et al., 2020; Reynolds, 2008).

4.1.2.1. GABAergic inhibitory signalling.

GABAergic signalling is critical for neurodevelopment and normal brain function. Further, pro-inflammatory cytokines, particularly IL-1β, IL-6 and TNFα, affect normal GABAergic synapse formation and reduce GABAergic interneuron density and GABAergic signalling currents (Crowley et al., 2016; El-Ansary and Al-Ayadhi, 2014). Imbalances in GABAergic function have been noted in a range of NDDs, including schizophrenia and ASD (Marotta et al., 2020; Reynolds, 2008) with delayed GABAergic maturation hypothesised to be a key factor of schizophrenia pathology (Hyde et al., 2011). Overall, the disturbances we observed for GABAergic candidate genes in this review were primarily tissue-specific (Fig. 10). However, such localised changes may have regional implications for GABAergic inhibition. Most studies demonstrated a significant decrease
in expression of Gad1 and Gad2 in the adult PFC. Likewise, the adult PFC was the only tissue identified with disturbances in GABAergic receptor expression. These results indicate a reduction in GABA synthesis and disturbed GABA signalling primarily in the PFC, a phenomenon identified in schizophrenia patients (Lewis et al., 2012; Lewis and Glausier, 2017). Of further note, a reduction in GABAergic interneurons, extensively studied in schizophrenia. The two studies evaluating Pvalb in this review identified no changes in RNA expression (Duchatel et al., 2019; Rahman et al., 2020). This parallels post-mortem analysis of brains of schizophrenia patients, with a recent meta-analysis finding no significant change in Pvalb RNA expression, but rather a reduction in Pvalb+ interneuron densities (Kaar et al., 2019).

These data therefore support the relevance of the mA model for the study of GABAergic dysfunction in schizophrenia biology.

### 4.1.2.2. Glutamatergic excitatory signalling

Glutamate is critical in synaptic plasticity and learning and memory processes (Willard and Koochekpour, 2013). However, excessive ionotropic glutamatergic signalling leads to excitotoxicity and neuronal death (Luján et al., 2005; Willard and Koochekpour, 2013). Mutations in Grin2a and 2b are linked with autism (Marotta et al., 2020), while schizophrenia animal models use inhibition of NMDA receptors for glutamatergic hypofunction (Cadina et al., 2018; Neill et al., 2010). Within this review, the glutamate transporters of the EAAT family were typically decreased when significant, while the glutamate ionotropic receptor subunits, Grin1, 2a and 2b changed in temporal-, tissue- and model-dependent patterns, with decreases in expression in early development and then increases in adulthood across both candidate and non-candidate studies (Fig. 10).

Taken together these data may support either an overall increase in glutamatergic signalling, or a compensation for a decrease in early developmental glutamatergic signalling. In any case, these results indicate the validity of the therapeutic relevance of glutamatergic mechanisms of schizophrenia, which are gaining broad interest in the clinical field (Howes et al., 2015), and support the mA model as a platform for exploring such pathways.

### 4.1.2.3. Dopaminergic signalling

Dopaminergic signalling is extensive in the mammalian brain and is notably involved in mood and reward behaviours, with elevated striatal dopamine a key pathological feature of schizophrenia (Boyd and Mailman, 2012). It is for this reason that schizophrenia treatment to date relies primarily on antipsychotic drugs (Boyd and Mailman, 2012; Meiser et al., 2013). However, despite evidence for the involvement of dopamine signalling in schizophrenia, results from this review have shown mostly non-significant changes in expression of dopaminergic genes (Fig. 10). However, while antipsychotic drugs remain the mainstay of antipsychotic treatment, it is well recognised that they are unable to ameliorate cognitive deficit and negative symptoms of schizophrenia. The lack of robust evidence for disturbed dopaminergic function in mA models to date could indicate alternative pathological changes underpinning offspring cognitive phenotypes within this paradigm, perhaps reflecting a particular patient subtype. Exploration of these alternative pathways in the mA model may therefore be of direct relevance to human cognitive symptoms, which are unaffected by dopaminergic modulation, aiding in a more complete understanding of disease biology and development of novel therapeutics for a personalised medicine approach.

### 4.1.3. Neurodevelopment

Neurodevelopmental candidate genes were poorly replicated with many non-significant results (Table 3). However, global expression studies identified a greater proportion of neurodevelopmental candidate genes when compared to the other two functional groups, with GO analysis significantly enriched for neurodevelopmental processes. This reiterates the relevance of neurodevelopmental genes in the pathology of the mA model. Indeed, inflammatory and neuronal signalling pathways are also inherently critical throughout brain development.

Across both candidate and non-candidate studies, neurodevelopmental genes involved in glial cell development and function displayed substantial consistencies in expression changes. Glial cells are the most abundant cell type in the brain and can be broadly divided into three groups: microglia, astrocytes and oligodendrocytes (Jäkel and Dimou, 2017). Microglia represent the resident immune cells of the brain (Jiang et al., 2018) while astrocytes interact with neuronal synapses and uptake/secret neurotransmitters (Kurotinski and Götz, 2002). Oligodendrocytes are important in neuronal myelination and have more recently been shown to support neuronal nutrient supplies (Philips and Rothstein, 2017). With their collective roles these cells are thus of increasing interest in NDD research, with disturbed glial cell biology a recognised factor of schizophrenia (Verhratsky and Parpura,
Fig. 10. Summary of results for neurotransmitter genes in mIA models in adult tissues. Figures summarise the changes in neurotransmitter genes in adult offspring brain tissues. Abbreviations: Pir C – Piriform Cortex, Par C – Parietal Cortex, Cer C – Cerebral Cortex, PFC – Prefrontal Cortex, Hipp – Hippocampus; Hypothal – Hypothalamus; Cpu – Caudate Putamen, CB – Cerebellum, NAc – Nucleus Accumbens, Olf Bulb – Olfactory Bulb, SN – Substantia Nigra; VTA – Ventral Tegmental Area, V Midbrain – Ventral Midbrain; N – no change in expression; ↑ – increased expression, ↓ – decreased expression. Figures were generated using BioRender.

2016). However, of the genes within this subgroup, it was those involved in myelination that have shown the most consistent changes in expression to date. Myelination is a predominantly postnatal process, and therefore the majority of genes within this subgroup are only disturbed postnatally (Table 3). However, oligodendrocyte progenitor cells are specified prenatally in mid-to-late gestation and thus are vulnerable to mIA (Fig. 4) with inflammatory processes shown to inhibit oligodendrocyte differentiation and promote hypomyelination (John et al., 2003). In support of this, most significant results for myelin genes showed a reduction in expression in postnatal offspring brains from both candidate and non-candidate driven approaches. This parallels the disturbed myelination and oligodendrocyte biology evidenced in schizophrenia (Flynn et al., 2003), and warrants further exploration into glial cell biology in the mIA model and in NDDs.

4.2. Epigenetic markers in mIA models and implications for NDD research

Epigenetic processes are of growing interest in complex brain disorders, due to their importance in normal brain development and ability to adapt to environmental stimuli (Jakovecvska and Akbarian, 2012; Millan et al., 2013). Critically, neuroepigenetic patterns can be programmable and hence may be mediating mechanisms by which mIA promotes transcriptomic changes and predisposes offspring to NDDs (Estes and McAllister, 2016; Millan et al., 2013). Despite this, only ten studies included in this review, exclusively performed in mouse-poly(I-C) models, have analysed epigenetic changes (Table 4). Nine of the 88 candidate genes (Mshp, Gad1, Gad2, Dcx1, Nr2f1, Nr4a2, Disc1, Slc17a7, Th) have been analysed for epigenetic patterns alongside gene expression and four of these genes (Gad2, Dcx1, Nr4a2, Disc1) have been identified in global methylation studies in schizophrenia (Wu et al., 2020). Importantly, these studies support the hypothesis of epigenetic-driven changes in gene expression arising from mIA-induced modulation of molecular pathways. Moreover, the overlap with epigenetic studies in schizophrenia patients and mIA models supports translatability to human health. Owing to the developmentally programmed nature of epigenetic mechanisms, further exploration of these markers could further our understanding of the sequential events underpinning the impact of mIA on offspring neurodevelopment. Understanding the epigenetic markers that are particularly critical in NDD pathology will be important for the identification of novel genes and pathways for early pharmacological intervention. Indeed, studies have indicated that traditional antipsychotics alter the epigenetic landscape while histone deacetylase inhibitors, like valproic acid, have been suggested as an adjuvant therapy to antipsychotics (Swathy and Banerjee, 2017).

4.3. Concluding remarks and future perspectives

Preclinical studies in the mIA model are critical for research into the underlying relationship between mIA and NDDs, essential for the development of improved and novel therapeutic strategies, particularly in different patient subtypes. In view of such long-term translational efforts it is particularly important for research groups to consider experimental justifications for methodological decisions and to consolidate results to inform robust mechanistic conclusions (Kentner et al., 2019; Roderick and Kenter, 2019). Our systematic review demonstrates the wealth of knowledge gained in the mIA field to date and substantiates the key role of transcriptomic and epigenomic mechanisms in mediating the downstream effects of mIA. Further, of the candidate genes demonstrating significant changes in expression, the direction of change typically accorded with that predicted based on the hypothesised pathology of NDDs, specifically: elevated inflammatory markers and glutamatergic receptor gene expression but reduced neurotrophic, myelin and GABAergic signalling gene expression. This illustrates the utility of the mIA model through its validation of mechanisms hypothesised to underly disease progression and may highlight key areas of therapeutic research. Hence, future research should aim to capitalise on the strengths of the mIA model as a preclinical tool. In particular, the mIA model has been shown to have credible constructive and face validity. Correlation of molecular outcome measures with both maternal inflammatory responses, which may contribute to some of the observed variation in outcome measures, and offspring behavioural phenotypes, could identify the molecular pathways that are particularly altered by maternal infection and thereby identify molecular factors which increase individual risk. In line with this, a true strength of the mIA model
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