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Placental omics and neuropsychiatric outcomes: A systematic review of longitudinal human studies

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ABSTRACT

The placenta is increasingly recognized as a key mediator between the prenatal environment and long-term neurodevelopment. Emerging omics studies suggest that placental molecular profiles may predict neuropsychiatric outcomes, yet evidence has remained fragmented and rarely synthesized in a longitudinal framework. Here we present the first systematic review of longitudinal placental omics studies with direct placenta-child linkage, encompassing epigenomic, transcriptomic, and metabolomic approaches. A systematic search of PubMed, Scopus, and PsycINFO identified twelve eligible studies (total n = 1752 placentas), all of which followed children from birth to neurodevelopmental assessment in early or middle childhood. Across studies, specific loci and metabolites varied, but convergent signals consistently implicated three biological domains: immune signaling, oxidative stress, and metabolic regulation. Representative findings included replicated epigenetic alterations at *DLL1*, nutrient- and genotype-sensitive variation at *CYP2E1* and *IRS2*, novel clusters at *NHIP*, transcriptomic integration involving *LRRFIP1*, environmentally responsive modules including *GALC, AUTS2*, and *CSMD1*, and metabolic shifts in fumarate, cystine, and 3-hydroxybutyrate. Notably, all longitudinal evidence to date centers on childhood outcomes, with the most robust associations reported for autism spectrum disorder, while links to schizophrenia and other adult psychiatric disorders remain speculative and are inferred indirectly from genetic or cross-sectional placental datasets. Together, these findings establish the placenta as a dynamic molecular interface where genetic background and environmental exposures converge to influence neurodevelopmental trajectories. By highlighting reproducible domains across omic layers, this review positions placental biology as a promising window into early biomarkers and mechanistic pathways of neuropsychiatric risk.

1. Introduction

According to the Developmental Origins of Health and Disease (DOHaD) hypothesis, the intrauterine environment plays a decisive role in shaping long-term health trajectories, with early-life perturbations predisposing individuals to chronic disease including psychiatric disorders later in life (O'Donnell and Meaney, 2017). Neurodevelopmental disorders (NDDs), including autism spectrum disorder (ASD) and attention-deficit/hyperactivity disorder (ADHD), affect up to 12 % of people worldwide, whereas schizophrenia (SCZ) has a lifetime prevalence of approximatively 1 % (Francés et al., 2022; Keepers et al., 2020). Taken together, these conditions affect roughly 9–13 % of the global population, underscoring the urgent need to investigate prenatal mechanisms of vulnerability.

The placenta is central to this trajectory. Beyond ensuring maternal-fetal exchange, it acts as an endocrine and neuroactive organ, producing

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hormones and neurotransmitters that directly influence fetal brain development (Rosenfeld, 2020). This "placenta-brain axis" (Kratimenos and Penn, 2019) mediates maternal-fetal crosstalk, with disruptions linked to altered neurogenesis, neuronal migration, and synaptic maturation (Vacher et al., 2021). Moreover, the placenta functions as a biological recorder of maternal exposures, including stress, diet, infection, and circadian disruption, leaving epigenetic and metabolic imprints that may persist into postnatal life and modulate psychiatric risk.

Recent evidence suggests that placental responses to maternal immune activation (MIA), metabolic alterations, or vascular stress can influence cortical development and contribute to ASD or SCZ vulnerability (Estes and McAllister, 2016). Similarly, maternal metabolic conditions such as obesity and gestational diabetes have been linked to changes in placental nutrient transport and mitochondrial function, thereby impacting fetal brain growth trajectories (Fitzgerald et al., 2020). Some studies have explored whether specific placental histopathology may be linked to long-term neuropsychiatric outcomes. For instance, a case-control study found that acute placental inflammation, chronic uteroplacental vasculitis, and maternal vascular malperfusion were significantly associated with increased risk of ASD (Straughen et al., 2017). Similarly, higher frequencies of trophoblast inclusions, microscopic abnormalities associated with aberrant villous development, have been found in placentas of children later diagnosed with ASD compared to controls (Anderson et al., 2007). However, other studies have reported no significant differences in gross placental morphology between ASD cases and controls, underscoring the heterogeneity of findings and the limitations of purely morphological approaches (Soullane et al., 2022). A growing body of research has also examined the role of the placenta in modulating the risk for SCZ. A subset of SCZ-associated risk genes has been shown to be preferentially expressed in the placenta, particularly in pregnancies complicated by early-life adversities such as preeclampsia and intrauterine growth restriction, suggesting that the penetrance of genetic liability is conditional on placental stress. These genes are enriched in placental tissues exposed to hypoxic and inflammatory stress and appear to predict SCZ only when such complications are present. Higher placental genomic risk scores have been associated with reduced neonatal brain volume and early cognitive deficits, especially in males. More recently, transcriptomic analyses have identified a group of placenta-enriched SCZ risk genes showing sex-biased expression in trophoblast subtypes, involved in nutrient sensing and cellular invasion pathways-mechanisms that may help explain individual differences in vulnerability (Ursini et al., 2023, 2021, 2018). These findings reinforce the notion that the placenta is not a passive conduit, but rather an active regulator that integrates maternal signals into developmental programming.

With the advent of multi-omics technologies, placental biology can now be interrogated with unprecedented depth. Importantly, these insights have led to the emerging concept of the placenta as both a diagnostic window and a potential target for intervention. Since placental tissue can be non-invasively accessed at birth, it offers a unique opportunity to identify biomarkers predictive of later psychiatric outcomes, which could be incorporated into precision-medicine approaches. Furthermore, understanding placental mechanisms may eventually inform maternal interventions, ranging from nutritional supplementation to circadian rhythm stabilization, that could mitigate fetal risk trajectories, though such applications remain speculative and require rigorous testing.

Some narrative reviews have addressed this framework, but to date no systematic review has synthesized longitudinal human studies linking placental omics to neurodevelopmental outcomes. It is important to note, however, that virtually all available longitudinal placental omics studies with direct child linkage focus on ASD, whereas evidence for SCZ or other psychiatric disorders remains indirect and primarily based on genetic enrichment or extrapolation from developmental parallels. To address this gap, we conducted a systematic review of longitudinal human studies investigating placental omics in relation to offspring neurodevelopmental and psychiatric outcomes. By integrating findings across epigenomic, transcriptomic, and metabolomic domains, our aim is to clarify convergent pathways, highlight current limitations, and outline directions for translational research.

2. Materials and methods

2.1. Protocol registration

This systematic review was prospectively registered in the PROSPERO international prospective register of systematic reviews (Registration ID: CRD42024615577). The protocol was developed following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (Page et al., 2021). This study involved the use of data from other studies and therefore did not require ethics approval as ethics approval was obtained in the original studies.

2.2. Eligibility criteria

Studies were eligible for inclusion if they investigated the association between placental molecular features, obtained through omics technologies, and subsequent neuropsychiatric outcomes in human populations. Eligible designs included prospective longitudinal cohorts and nested or retrospective case-control studies. Only investigations analyzing placental samples collected during gestation or at delivery and directly linked to children with clinically assessed neuropsychiatric outcomes, were considered. Cross-sectional, case-only, or studies lacking longitudinal child follow-up were excluded. The molecular modalities of interest encompassed any omics technologies applied to placental tissue, including genomics, epigenomics, transcriptomics, proteomics, metabolomics, or multi-omics combinations. To be included, studies were required to report outcomes related to clinically diagnosed psychiatric conditions, such as ASD, ADHD, SCZ, bipolar disorder (BD), or major depressive disorder (MDD). Diagnoses had to be made using standardized criteria such as DSM or ICD diagnostic systems. Studies relying exclusively on screening tools, parental questionnaires, or self-reported outcomes without clinical confirmation were excluded. Only peer-reviewed studies available in full text and published in English were eligible. Exclusion criteria included studies based solely on animal models or in vitro experiments, studies not employing longitudinal or case-control designs, reviews or opinion articles without original data, and studies that did not specifically examine placental omics features in relation to neuropsychiatric outcomes.

2.3. Information sources and search strategy

A comprehensive search of three electronic databases, PubMed, Scopus, and PsycINFO, was conducted to identify relevant studies published between January 2000 and May 2025. The search strategy combined controlled vocabulary (e.g., MeSH terms) and free-text keywords relating to placental omics and neuropsychiatric disorders. The following search string was developed for PubMed and adapted accordingly for Scopus and PsycINFO (see supplementary material 1):

(epigenomics OR methylation OR exposure OR transcriptome OR genetic OR multiomics) AND (placenta) AND (schizophrenia OR bipolar disorder OR depression OR autism OR Attention-Deficit/Hyperactivity Disorder OR ADHD).

No filters were applied for study type, but only articles published in English and involving human participants were retained during the selection process. Search syntax was adapted for each database's indexing system. The final search yielded a total of 1512 records: 553 from PubMed, 825 from Scopus, and 150 from PsycINFO. The review focused on psychiatric and neurodevelopmental conditions to align with its aim of elucidating placental molecular pathways contributing to psychiatric vulnerability and behavioral outcomes. Conditions typically addressed within neurological or neurogenetic frameworks, such as intellectual

disability and movement disorders, were considered outside this conceptual scope.

2.4. Study selection

All retrieved records were imported into a reference management software (Ouzzani et al., 2016), and 533 duplicates were removed. The remaining 979 articles underwent an initial screening of titles and abstracts by two independent reviewers to assess relevance and compliance with the eligibility criteria. Studies deemed potentially eligible were then assessed in full text. Discrepancies at either screening stage were resolved through discussion and consensus, with the involvement of a third reviewer if necessary. A total of 12 studies met all inclusion criteria and were included in the final synthesis.

2.5. Data collection process

A standardized data extraction form was developed and piloted to systematically collect relevant information from each included study. For each article, the following data were extracted: study design, cohort name or origin, sample size, omics modality and technology used, timing and nature of placental sampling, type of adverse prenatal exposure (if reported), neuropsychiatric outcomes assessed, diagnostic tools and follow-up age, main molecular findings, and associated biological pathways or functions. Extraction was performed independently by two reviewers, and disagreements were resolved by consensus.

2.6. Data items

The primary data item of interest was the presence of statistically significant associations between placental omics signatures and clinically assessed neuropsychiatric outcomes. Where available, specific gene names, epigenetic loci (e.g., differentially methylated regions), transcriptomic targets, or metabolites were recorded, along with any reported interaction with environmental exposures such as maternal stress, pollutants, or nutritional factors. Biological functions and pathway enrichments were noted when reported by the authors.

2.7. Risk of bias and quality assessment

The methodological quality of the included studies was evaluated using the NIH Quality Assessment Tool for Case–Control Studies ("Study Quality Assessment Tools | NHLBI, NIH," n.d.). Two independent reviewers conducted the assessment, with disagreements resolved by consensus. The tool comprises 12 items assessing study design, including clarity of the research question, definition and selection of cases and controls, comparability of groups, ascertainment of exposure, blinding of outcome assessment, sample size justification, and control for confounding. Overall, none of the 12 included studies were rated as poor quality. Seven studies were judged as Good, primarily reflecting clear research questions, standardized diagnostic criteria, prospective biospecimen collection, and adequate exposure assessment. The remaining studies were rated as Fair, mainly due to incomplete adjustment for confounders, lack of sample size justification, and limited information on blinding of laboratory analyses. Common methodological limitations included: insufficient reporting of matching between cases and controls; inconsistent handling of potential confounders such as maternal psychiatric history, obstetric complications, or environmental exposures; and absence of explicit power calculations. Nonetheless, most studies provided detailed case definitions and robust molecular analyses, supporting their inclusion in the synthesis. A study-level summary of quality ratings is provided in Supplementary Table S1–2.

2.8. Synthesis methods

Due to the heterogeneity in study design, omics platforms, outcome measures, and analytical approaches, a meta-analysis was not feasible. Instead, a narrative synthesis approach was employed to summarize key findings across studies. Where possible, biological pathways and mechanisms implicated in neurodevelopment were integrated and discussed. The results were stratified by methodological domain (e.g., DNA methylation, transcriptomics, metabolomics) and contextualized within the scope of environmental exposures and developmental timing.

2.9. Data availability

Data used (means, effect sizes, standard deviations and confidence intervals) can be obtained from the original studies in the systematic review, listed in Table 1. Databases searched included PubMed, Scopus and PsycINFO.

3. Results

3.1. Study selection

A total of 1512 records were retrieved from three electronic databases: PubMed (n = 553), Scopus (n = 825), and PsycINFO (n = 150). After removing 533 duplicates, 979 unique records were screened based on title and abstract. Of these, 54 articles underwent full-text assessment, and 12 studies ultimately met all eligibility criteria and were included in the review. The study selection process followed PRISMA 2020 guidelines and is summarized in the flow diagram (Fig. 1).

3.2. Study characteristics

All included studies adopted either prospective cohort or nested case-control designs and focused on human placental samples collected during pregnancy or at birth. Most were derived from well-established longitudinal cohorts, such as MARBLES, EARLI, and ELGAN, with neurodevelopmental follow-up assessments performed predominantly at 36 months, though two studies extended follow-up to 10 years. Across all studies, a total of 1752 placental samples were analyzed. Because several investigations drew on overlapping cohorts this figure may include some duplicate cases, but it represents the full sample of placentas with direct child linkage reported to date. The majority of participants were selected based on high familial risk for ASD or preterm birth, and neuropsychiatric outcomes were assessed using standardized diagnostic tools including DSM-IV/5, Autism Diagnostic Observation Schedule (ADOS), Mullen Scales of Early Learning (MSEL), and Autism Diagnostic Interview–Revised (ADI-R). Importantly, no study evaluated adult psychiatric conditions such as SCZ or BD.

3.3. Epigenomic findings

Epigenomic investigations, using whole genome bisulfite sequencing (WGBS) and high-density arrays, represented the most frequent methodological approach (Table 1). Early work by Schroeder et al. (2016) identified increased methylation near *DLL1* in ASD placentas, implicating a locus involved in neurogenesis and immune development (Schroeder et al., 2016). This finding was subsequently replicated by another study, making *DLL1* the only locus consistently identified across independent placental epigenomic studies. That work also identified genome-wide significant DMRs at *CYP2E1* and *IRS2*, shaped by genetic variation and maternal prenatal vitamin intake, respectively (Zhu et al., 2019). More recently, the same group identified a robust hypomethylated cluster at NHIP, a primate-specific gene downregulated in both placenta and ASD postmortem brain, and co-expressed with ASD-related genes such as FOXG1 and NR3C2 (Zhu et al., 2022).

Complementary array-based studies revealed thousands of differentially methylated CpGs, highlighting markers in *GRIPAP1, NOS1AP, MOSPD1,* and *ZNF217 (*Bahado-Singh et al., 2022, 2021*)*. Pathway analyses emphasized synaptogenesis and cortical differentiation. By

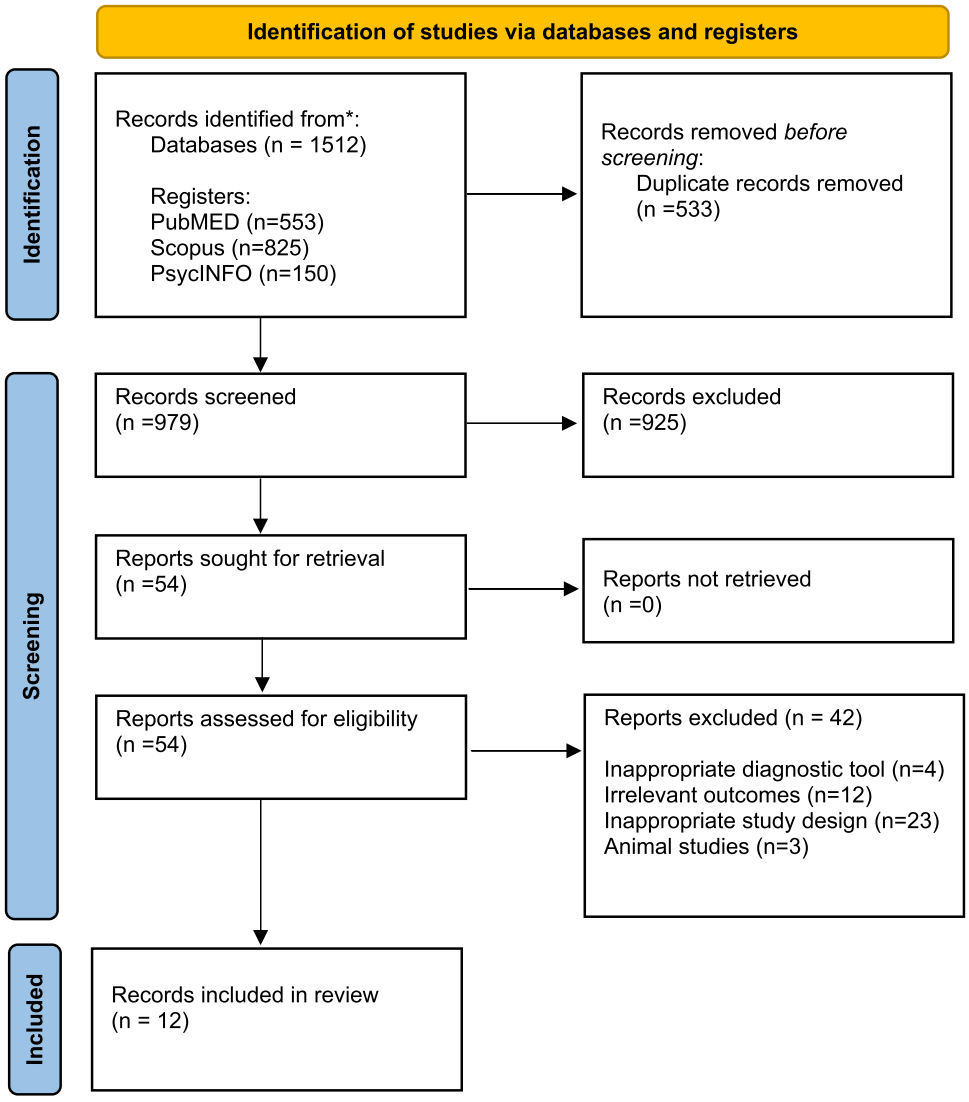

Fig. 1. The PRISMA Flow diagram.

contrast, Schmidt et al. (Schmidt et al., 2016) and Bakulski et al. (Bakulski et al., 2021) did not identify genome-wide significant loci, though enrichment was observed in SFARI-curated ASD genes (Table 2) and pathways related to adhesion, histone demethylation, and nucleotide biosynthesis. Cross-compartmental correlations suggested shared epigenetic signatures between maternal and fetal sides of the placenta.

3.4. Transcriptomic and multi-omic findings

Beyond DNA methylation, transcriptomic and integrative approaches provided additional insights. Freedman et al., identified 111 genes associated with ASD outcomes at 10 years in the ELGAN cohort, including *EWSR1, ATF7IP,* and *DDX59*. Overlap with miRNA and epigenetic regulation suggested convergence on immune modulation, with *LRRFIP1* emerging as a key locus (Freedman et al., 2023). Santos et al., integrated mRNA, CpG methylation, and miRNA data in preterm infants, linking placental *HECA* and *LMO4* to Social Responsiveness Scale (SRS) scores, while *RAB5A, TMEM167A, ITPRIPL2,* and *STAT2* associated with IQ. Integration across molecular layers (e.g., methylation at *CHST11*) predicted neurodevelopmental outcomes, and cell-type-specific analyses revealed distinct contributions of stromal versus syncytiotrophoblast compartments (Santos et al., 2020). Environmental exposures emerged as critical modulators of these placental signatures. Mouat et al., combined WGBS with co-methylation network analysis and demonstrated that maternal polychlorinated biphenyls (PCBs) exposure influenced DNA methylation modules involving *GALC*, *AUTS2*, and *CSMD1*. These networks were associated with both exposure levels and neurodevelopmental outcomes, with lower methylation in the *GALC* module linked to increased ASD risk (Mouat et al., 2023). The findings highlighted lipid metabolism, immune function, and synaptic development as environmentally sensitive pathways shaping risk.

3.5. Metabolomic findings

Metabolomic studies further highlight the placenta's integrative role as a molecular interface between maternal exposures and fetal neurodevelopment. For instance, Parenti et al. (2022) (Parenti et al., 2022), reported that prenatal exposure to phthalates was associated with altered placental metabolites such as fumarate, cystine, and uridine. Although this finding originates from an exposure context, its relevance lies in demonstrating that maternal environmental factors can shape placental metabolic states later linked to neurodevelopmental outcomes, underscoring the placenta's biosensing and signaling functions. In a subsequent study, elevated 3-hydroxybutyrate (3-OHB) was linked to non-typically developing (non-TD) but not ASD outcomes (Parenti et al., 2024), suggesting divergence in metabolic pathways across

Table 1
Main findings.

Reference	Study Design	Sample Size (total/ placenta)	Omics	Method	Adverse Early Life Exposure	Diagnostic tools /age at diagnosis	Main Statistically Significant Findings	Associated Biological Functions
Parenti et al. (2024)	Prospective nested case-control study (MARBLES)	ASD: 45 Non-TD:19 TD: 87 PLA: 141	Metabolomics (NMR)	^{1}H-NMR metabolomics	High familial ASD risk	ADOS, MSEL 36 Months	3-OHB levels in placenta and cord serum linked to non-TD but not ASD;	Lipid metabolism and oxidative stress identified as key metabolic pathways involved in atypical development.
Freedman et al. (2023)	Prospective nested case-control study (ELGAN)	ASD: 28 TD: 340 PLA: 368	Multi-omics (Transcriptomics, Epigenomics)	Illumina EPIC BeadChip array + RNA-Seq + miRNA-Seq	Preterm birth	ADOS−2 10 Years	111 placental genes were differentially expressed comparing ASD with healthy controls. 15 genes showed significant ($p < 0.05$) predictive ORs consistent with expression changes. Key genes such as EWSR1 (OR: 6.57), ATF7IP (OR: 3.45), and DDX59 (OR: 2.84) were strongly linked to increased ASD risk. Furthermore, 8.1 % of ASD-associated genes showed CpG methylation changes, and 12.6 % were regulated by miRNAs, including LRRFIP1, which is influenced by both epigenetic mechanisms (OR: 0.42).	Pathway analysis revealed that these genes are involved in chromatin regulation, immune response, and neuroinflammatory processes. **EWSR1**: RNA binding, transcriptional regulation, oncogenesis**ATF7IP**: Histone modification, immune response regulation**DDX59**: RNA helicase activity, neurodevelopment, neuronal function**LRRFIP1**: Immune modulation, inflammation regulation, neuroprotection
Mouat et al. (2023)	Prospective nested case-control study (MARBLES)	ASD: 52 Non-TD: 21 TD: 74 PLA: 147	Epigenomics (WGBS)	Whole genome bisulfite sequencing + WGCNA	Maternal PCBs exposure	ADOS, ADI-R, MSEL, DSM−5 36 Months	Placental DNA co-methylation modules are correlated with child neurodevelopment and map to genes previously associated with ASD: GALC, AUTS2, CSMD1. Only the GALC module negatively correlated with ASD diagnosis, suggesting that less methylation at GALC may be associated with a higher risk of ASD. Two placental DNA methylation modules, mapped to AUTS2 and CSMD1, were associated with both maternal PCB exposure and child neurodevelopment.	**GALC**: Lipid metabolism regulation, myelination. **AUTS2**: Neuronal plasticity, synaptic development, transcriptomics. **CSMD1**: Immune response, neuroinflammation
Bahado-Singh et al. (2022)	Retrospective case-control study	ASD: 10 TD: 10 PLA:20	Epigenomics (DNA methylation)	Illumina HumanMethylation450 BeadChip + AI	Preterm birth	DSM-IV Not reported	In ASD, 4870 intragenic and 2041 intergenic sites were differentially methylated. Top intragenic hits included CLPTM1, LOC283267, KIAA1530, AGAP1, and MAD1L1. AI-based models identified markers in NRN1, ZNF217, GPNMB, NKX2–5, and ZNF267 that showed high predictive performance (AUC = 1.00). Among these, ZNF217 consistently ranked among the top features across deep learning and random forest analyses, along with additional genes such as HYMAI, PLAGL1, RPS6KA2, ZNF385D, and GABBR1, as well as several non-genic regions.	IPA revealed enrichment in pathways related to cerebral cortex development, neurodevelopmental disorders, neuronal differentiation, cognitive impairment, and synaptogenesis **NRN1**: Neuronal growth, synaptic plasticity **GABBR1**: GABAergic signaling, synaptic transmission **RPS6KA2**: MAPK signaling, cell growth, differentiation, and stress response **ZNF385D** DNA binding, language development, and cognitive processes **AGAP1**: Endosomal trafficking, neurite outgrowth **ZNF217**: Transcriptional regulation, cell proliferation, apoptosis inhibition **ZNF267**: Gene regulation, zinc finger transcription

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Table 1 (*continued*)

Reference	Study Design	Sample Size (total/ placenta)	Omics	Method	Adverse Early Life Exposure	Diagnostic tools /age at diagnosis	Main Statistically Significant Findings	Associated Biological Functions
								HYMAI: Imprinted gene regulation, transient neonatal diabetes mellitus **PLAGL1**: Cell growth suppression, transcriptional regulation, and diabetes mellitus **NKX2–5**: Heart development, cardiac conduction, and transcriptional regulation **MAD1L1:** Cell cycle regulation, tumor suppression, chromosomal stability **GPNMB**: Melanogenesis, tissue repair, and cell adhesion **CLPTM1**: Apoptosis regulation, neuronal signaling **KIAA1530**: DNA repair, transcription-coupled nucleotide excision repair **LOC283267**: Uncharacterized; potential regulatory role
Zhu et al. (2022)	Prospective nested case-control study MARBLES + EARLI	ASD: 83 Non-TD: 13 TD: 108 Pla:204	Epigenomics (WGBS) + Genomics (WGS)	Whole genome bisulfite sequencing	High familial ASD risk	ADOS, DSM-V, MSEL, ADI-R 36 Months	The study identified 134 placental DMRs distinguishing ASD from TD (77 hypermethylated, 57 hypomethylated), mapping to 183 genes. A cluster of 12 hypomethylated DMRs at 22q13.33 was consistently replicated and correlated with ASD severity. This region overlapped *NHIP*, a gene with reduced placental and brain expression in ASD. The 22q13.33 SV was associated with lower DNA methylation at this locus, reduced *NHIP* expression in both placenta and postmortem brain tissue, and increased ASD risk. Early prenatal vitamin use was linked to increased methylation at the 22q13.33 locus, suggesting a potential protective effect against ASD.	**NHIP** (RNA gene)**:** Hypoxia response, placental development, transcriptional regulation Expression correlates with synaptic and neurodevelopmental genes, including ASD risk loci such as *FOXG1*, *NR3C2*, and *NR2F1*.
Parenti et al. (2022)	Prospective cohort study (EARLI)	ASD: 32 Non-TD: 17 TD: 83 Pla: 132	Metabolomics (NMR)	^{1}H NMR metabolomics	Prenatal phthalate exposure	ADOS, MSEL 3 Years	The placental metabolome showed an association with neurodevelopmental outcomes only in male children, suggesting a possible sex-specific effect. Several metabolites were nominally associated with neurodevelopment in males but not in females. For example, fumarate, cystine and uridine. However, none of these associations remained statistically significant after FDR correction.	Citric acid cycle, redox regulation, and lipid metabolism (sex-specific associations in males).
Bahado-Singh et al. (2021)	Retrospective case-control study	ASD: 14 TD: 10 Pla: 24	Epigenomics (DNA methylation)	Illumina HumanMethylation450 BeadChip + AI (DL, RF)	None (full-term neonates)	DSM-IV Not reported	In ASD, 6853 intragenic (4129 genes) and 2802 intergenic CpGs were differentially methylated. Top 5 differentially methylated CpGs: cg16699528 (*GATS*; *PVRIG*), cg15436096 and cg21893185 (*GPR135*), cg19949776	IPA revealed enrichment in pathways related to quantity of synapse, microtubule dynamics, neuritogenesis and abnormal morphology of neurons. **GATS**: cell proliferation, migration. **PVRIG**: Immune regulation, T cell

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Table 1 (*continued*)

Reference	Study Design	Sample Size (total/ placenta)	Omics	Method	Adverse Early Life Exposure	Diagnostic tools /age at diagnosis	Main Statistically Significant Findings	Associated Biological Functions
							(LOC100132724; *AP4E1*) and cg13342370 (*ITGBL1*). The top 5 AI-based predictive markers were, cg23920016 (*NOS1AP*), cg24274662 (*MOSPD1*), cg05036212 (intergenic) cg26017408 (*AFAP1L2*) and cg16930349 (*GRIPAP1*).	signaling, cell surface receptor activity; **GPR135**: GPCR signaling, intracellular trafficking, receptor interaction; **LOC100132724**: Uncharacterized; **AP4E1**: Vesicle-mediated transport, protein sorting, membrane trafficking; **ITGBL1**: Cell adhesion, extracellular matrix organization, protein-protein interaction; **NOS1AP**: Signal transduction, protein binding, cytoskeletal regulation; **MOSPD1**: Transcription regulation, cell differentiation, structural molecule activity; **AFAP1L2**: Signal transduction, cytoskeleton organization, gene expression regulation; **GRIPAP1**: Endosomal trafficking, synaptic regulation, signal transduction;
Bakulski et al. (2021)	Prospective nested case-control study (MARBLES)	ASD: 33 Non-TD: 96 TD: 73 Pla: 202	Epigenomics	Illumina HumanMethylation450 BeadChip	High familial ASD risk	DSM−5 36 months	- No individual CpG sites reached genome-wide significance for association with ASD after adjusting for multiple comparisons. -Individual DNA methylation sites nominally associated with ASD ($P < 0.05$) in each tissue were highly enriched for SFARI genes. - Effect estimates for the different tissues were most highly correlated between fetal and maternal side placenta ($r = 0.35$).	The biological processes with lowest rank sum across the five tissues were cell adhesion (rank sum of 4466), histone H3-K36 demethylation (rank sum of 4485) and regulation of nucleotide biosynthetic process (rank sum 4594), though none of these processes had at least $p < 0.05$ in all five tissues.
Santos Jr. et al. 2020	Prospective nested case-control study ELGAN	ASD: 35 TD: 344 Pla:379	Epigenomics, Transcriptomics; (Genome-wide mRNA, CpG methylation and miRNA)	Genome wide mRNA: Illumina Hiseq 2500; CpG metilation: HTG EdgeSeq; miRNA: Illumina EPIC/ 850 K array;	Extreme prematurity	SRS, IQ (DAS), ADI-R, ADOS−2 10 Years	- *HECA* and *LMO4* expression associated with SRS;- *RAB5A*, *TMEM167A*, *ITPRIPL2*, *STAT2* mRNA expression associated with IQ;- cg09418354 (within *CHST11*) linked to IQ; - No CpGs or miRNAs associated with SRS; - No miRNAs associated with IQ; - Two stromal cell-specific genes (*BRD2* and *ZNF618*) associated with SRS; - Two syncytiotrophoblast-specific genes (*ATP2B1* and *FAM126A*) associated with IQ;	Enrichment analysis revealed that genes associated with IQ are involved in membrane organization processes, while those linked to SRS are enriched in nucleic acid and enzyme binding functions. **HECA**: Cell cycle regulation, epithelial tube development, cancer-related processes; **LMO4**: Transcription regulation, neural development, oncogenesis; **RAB5A**: Vesicle trafficking, endocytosis regulation, exosome release; **TMEM167A**: Secretory pathway regulation, Golgi apparatus function; **ITPRIPL2**: Membrane localization, potential signaling regulation; **STAT2**: Immune regulation, antiviral response, transcription activation; **CHST11**: Sulfation of chondroitin, cartilage proteoglycan biosynthesis, extracellular matrix organization; **BRD2**: Transcription regulation, chromatin remodeling, immune

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Table 1 (*continued*)

Reference	Study Design	Sample Size (total/ placenta)	Omics	Method	Adverse Early Life Exposure	Diagnostic tools /age at diagnosis	Main Statistically Significant Findings	Associated Biological Functions
								modulation; **ZNF618**: Transcription regulation, DNA binding, chromatin interaction; **ATP2B1**: Calcium transport, vascular tone regulation, bone mineralization; **FAM126A (HYCC1)**: Myelination, phosphoinositide signaling, oligodendrocyte development;
Zhu et al. (2019)	Prospective nested case-control study MARBLES	ASD: 20 TD: 21 Pla: 41 (all males)	Epigenomics (WGBS)	Whole genome bisulfite sequencing	High familial ASD risk	ADOS, DSM−5 36 months	- The study identified 400 placental DMRs distinguishing ASD from TD (296 hypermethylated, 104 hypomethylated), mapping to 596 genes. - Differential methylation at *DLL1* in ASD placenta was replicated from a prior study (Schroeder et al. 2016); - Placenta DMR genes were enriched in ASD risk genes. A significant overlap of 39 genes was identified between placenta ASD DMRs and SFARI ASD risk genes. - Of the 400 ASD DMRs, 2 reached genome-wide significance, located inside *CYP2E1* (hypomethylated) and *IRS2* (hypermethylated) genes; -*CYP2E1* DMR methylation associated with ASD and rs1536828 genotype, with homozygous G/G samples showing lowest methylation; rs1536828 genotype not associated with ASD diagnosis; -*IRS2* methylation unaffected by genotype but influenced by maternal prenatal vitamin use.	- Placenta ASD DMRs were enriched for transcription, protein modification, embryonic organ development and neuron fate commitment; - The 39 common genes were enriched for positive regulation of histone H3K4 methylation, multicellular organ development, and system development. **CYP2E1**: drug metabolism, lipid synthesis, and xenobiotic oxidation. **IRS2**:glucose homeostasis, growth, and cell cycle regulation. **DLL1**:neuronal differentiation, immune system development, and tissue morphogenesis.
Schroeder et al. (2016)	Prospective nested case-control study MARBLES	ASD: 24 TD:23 Pla: 47	Epigenomics (WGBS)	Whole genome bisulfite sequencing (MethylC-seq)	High familial ASD risk	ADOS, DSM-IV/5 36 months	- HMD containing a putative fetal brain enhancer near *DLL1* was significantly higher methylated in ASD. - No significant differences in overall methylation levels, including CpG island regions, were observed between ASD and typical placentas.	**DLL1**:neuronal differentiation, immune system development, and tissue morphogenesis
Schmidt et al. (2016)	Prospective nested case-control study MARBLES	ASD: 24 TD:23 Pla: 47	Epigenomics (WGBS)	Whole genome bisulfite sequencing (MethylC-seq)	High familial ASD risk; Environmental exposures	ADOS, DSM-IV/5 36 months	No significant overall differences in placental methylation patterns between ASD and TD were observed.	NA

Abbreviations: *AFAP1L2*, Actin Filament Associated Protein 1 Like 2; *AGAP1*, ArfGAP With GTPase Domain, Ankyrin Repeat And PH Domain 1; *AP4E1*, Adaptor Related Protein Complex 4 Subunit Epsilon 1; *ADOS*, Autism Diagnostic Observation Schedule; *ADOS-2*, Autism Diagnostic Observation Schedule, Second Version; *ADI-R*, Autism Diagnostic Interview–Revised; *ASD*, Autism Spectrum Disorder; *ATF7IP*, Activating Transcription Factor 7-Interacting Protein 1; *ATP2B1*, ATPase Plasma Membrane Ca2 + Transporting 1; *AUTS2*, Activator Of Transcription And Developmental Regulator AUTS2; *BRD2*, Bromodomain Containing 2; *CHST11*, Carbohydrate Sulfotransferase 11; *CLPTM1*, Regulator Of GABA Type A Receptor Forward Trafficking; *CpG*, Cytosine-phosphate-Guanine; *CSMD1*, CUB And Sushi Multiple Domains 1; *CYP2E1*, Cytochrome P450 Family 2 Subfamily E Member 1; *DAS-II*, School-Age Differential Ability Scales-II; *DDX59*, DEAD-Box Helicase 59; *DLL1*, Delta Like Canonical Notch Ligand 1; *DMRs*, Differentially Methylated Regions; *EWSR1*, Ewing Sarcoma Breakpoint Region 1; *FAM126A (HYCC1)*, Hyccin PI4KA Lipid Kinase Complex Subunit 1; *FOXG1*, Forkhead Box G1; *GALC*, Galactosylceramidase; *GABBR1*, Gamma-Aminobutyric Acid Type B Receptor Subunit 1; *GATS*, GATS protein-like; *GPCR*, G Protein-Coupled Receptor; *GPNMB*, Glycoprotein Nmb; *GPR135*, G Protein-Coupled Receptor 135; *GRIPAP1*, GRIP1 Associated Protein 1; *HECA*, Hdc Homolog, Cell Cycle Regulator; *HMD*, High Methylated Domain; *HYMAI*, Hydatidiform Mole Associated And Imprinted; *IQ*, Intellectual Ability; *IRS2*, Insulin Receptor Substrate 2; *ITGBL1*, Integrin Subunit Beta Like 1; *ITPRIPL2*, ITPRIP Like 2; *KIAA1530*, UV-stimulated scaffold protein A; *LMO4*, LIM Domain Only 4; *LOC283267*, Gene of unknown function, temporarily classified as a locus (LOC) in the human genome; *LRRFIP1*, LRR Binding FLII Interacting Protein 1; *MAD1L1*, Mitotic Arrest Deficient 1 Like 1; *miRNAs*, microRNAs; *MOSPD1*, Motile Sperm Domain Containing 1; *MSEL*, Mullen Scales of Early Learning; *NA*, Not Available; *NHIP*, Neuronal Hypoxia Inducible Placenta Associated;

neurodevelopmental subgroups. Although many associations did not withstand multiple-testing correction, consistent signals implicated oxidative stress and lipid metabolism in placental contributions to brain development.

3.6. Summary and convergent pathways

Across omic layers, longitudinal placental studies reveal reproducible molecular associations with neurodevelopment. While the specific loci and metabolites vary across platforms and cohorts, a consistent pattern emerges: epigenomic, transcriptomic, and metabolomic signatures converge on a limited set of biological domains, namely immune signaling, oxidative stress, and metabolic regulation (Fig. 2). These domains appear sensitive to both genetic background and environmental exposures, and together define placental states that prospectively predict neurodevelopmental outcomes, with the strongest evidence for ASD, but also extending to cognitive and behavioral variation.

4. Discussion

This systematic review was designed to examine placental molecular markers associated with neuropsychiatric outcomes across the lifespan, with particular emphasis on longitudinal multi-omic studies that incorporate data enabling the linkage of each individual to the specific placenta from which they were born. Our analysis revealed a striking absence of studies directly linking placental biology to psychiatric outcomes emerging in adulthood. Available longitudinal evidence is almost entirely focused on ASD, supported by well-characterized cohorts and placenta-child linkage designs. By contrast, insights into SCZ and other adult psychiatric disorders are extrapolated indirectly from genetic studies and cross-sectional placental datasets, and therefore remain speculative.

Despite this asymmetry, the reviewed literature provides compelling evidence for the placenta's critical role in shaping early neurodevelopmental trajectories. The studies summarized in Table 1 demonstrate that placental DNA methylation, gene expression, and metabolomic signatures are sensitive to both genetic and environmental variation, and are measurably associated with neurodevelopmental outcomes such as ASD diagnosis, social behavior, and cognitive ability. Furthermore, the enrichment of several placental methylation signals in genes curated by SFARI (Table 2) reinforces the placenta's involvement in early ASD biology and suggests mechanistic continuity between placental and brain molecular landscapes. To further contextualize these findings, the following sections explore in greater detail the molecular mechanisms that may mediate these associations and propose an integrative interpretative framework grounded in placental systems biology.

A key question emerging from these findings is how molecular changes in the placenta can exert long-lasting influences on brain development and psychiatric vulnerability. One plausible mechanism involves the placenta's role in buffering or amplifying prenatal stress signals, originating from the maternal environment, which subsequently influence fetal neurodevelopment through epigenetic modifications of placental genes involved in nutrient transport, immune and endocrine function, as well as genes directly implicated in neurodevelopment (Fig. 3). Importantly, these effects are likely to be highly dependent on developmental timing. Distinct neuroanatomical structures follow specific maturational trajectories during gestation, and evidence suggests that key regions involved in psychiatric disorders, such as the prefrontal cortex, begin developing as early as the first trimester and remain particularly vulnerable to insults throughout the second and third trimesters, when critical processes such as neuronal migration, cortical lamination, and synaptogenesis take place (Kostović et al., 2021; Selemon and Zecevic, 2015). Placental molecular alterations during these critical windows could thus impact neurogenesis, synapse development, and circuit wiring in ways that are not easily compensated postnatally,

NKX2–5, NK2 Homeobox 5; *NON-TD*, Non-Typical Development; *NOS1AP*, Nitric Oxide Synthase 1 Adaptor Protein; *NR2F1*, Nuclear Receptor Subfamily 2 Group F Member 1; *NR3C2*, Nuclear Receptor Subfamily 3 Group C Member 2; *NRN1*, Neuritin 1; *PCBs*, Polychlorinated Biphenyls; *PLA*, Placenta; *PLAGL1*, PLAG1 Like Zinc Finger 1; *PVRIG*, PVR Related Immunoglobulin Domain Containing; *RAB5A*, RAB5A Member RAS Oncogene Family; *RPS6KA2*, Ribosomal Protein S6 Kinase A2; *SRS*, Social Responsiveness Scale; *SFARI*, Simons Foundation Autism Research Initiative; *STAT2*, Signal Transducer And Activator Of Transcription 2; *SV*, Structural Variant; *TD*, Typical Development; *TMEM167A*, Transmembrane Protein 167A; *TPRIPL2*, ITPRIP Like 2; *WGBS*, Whole Genome Bisulfite Sequencing; *WGS*, Whole Genome Sequencing; *ZNF217*, Zinc Finger Protein 217; *ZNF267*, Zinc Finger Protein 267; *ZNF385D*, Zinc Finger Protein 385D; *ZNF618*, Zinc Finger Protein 618; *3-OHB*, 3-Hydroxybutyrate; *1H NMR*, Proton Nuclear Magnetic Resonance; *DESeq2*, Differential expression analysis based on the negative binomial distribution; *FDR*, False Discovery Rate.

Table 2
Cross-reference between main placenta-associated ASD candidate genes and the SFARI Gene Scoring database.

Gene	Chromosome	SFARI Gene Scoring	SFARI Score	Category	Notes
AFAP1L2	10	No	–	–	Actin cytoskeleton regulation; placenta-identified biomarker
AGAP1	2	Yes	2	Strong candidate	Involved in endosomal trafficking; neuronal process regulation
AP4E1	15	No	–	–	Involved in vesicle-mediated protein sorting
ATF7IP	17	No	–	–	Histone methylation regulator; immune response modulation
ATP2B1	12	No	–	–	Calcium pump expressed in placenta and brain; regulates trophoblast invasion and angiogenesis; de novo variants linked to neurodevelopmental delay and ASD.
AUTS2	7	Yes	1	Strong candidate	Implicated in neuronal development; also associated with ASD brain tissue
BRD2	6	No	–	–	Transcription/chromatin regulator; placenta-expressed
CHST11	12	No	–	–	Cartilage proteoglycan sulfation; extracellular matrix
CLPTM1	5	No	–	–	Apoptosis and neuronal signaling regulator
CSMD1	8	Yes	2	Strong candidate	Complement regulation; neuroimmune functions; large brain-expressed protein
CYP2E1	10	No	–	–	Xenobiotic metabolism
DDX59	1	No	–	–	RNA helicase; neurodevelopment function
DLL1	6	Yes	2	Syndromic	Consistently found in placenta DMRs; also replicated across studies
EWSR1	22	No	–	–	Strong OR in transcriptomic study; involved in chromatin remodeling
FAM126A	7	No	–	–	Oligodendrocyte myelination; phosphoinositide signaling
GABBR1	6	No	–	–	GABAergic synaptic transmission;
GALC	14	No	–	–	Potential novel placental candidate; involved in lipid metabolism and myelination
GATS	22	No	–	–	Cell proliferation and migration
GPNMB	7	No	–	–	Tissue repair, adhesion marker
GPR135	14	No	–	–	Receptor signaling; intracellular trafficking
GRIPAP1	X	No	–	–	Endosomal trafficking; synaptic regulation
HECA	6	No	–	–	Cell cycle and epithelial development
HYMAI	6	No	–	–	Imprinted gene; neonatal metabolic regulation
IRS2	13	No	–	–	Linked to metabolic signaling; methylation modulated by vitamin intake
ITGBL1	13	No	–	–	ECM adhesion; extracellular matrix organization
ITPRIPL2	16	No	–	–	Membrane signaling; localization regulator
KIAA1530	6	No	–	–	DNA repair; transcription-coupled excision repair
LMO4	1	No	–	–	Neural development transcription modulation
LRRFIP1	2	No	–	–	Immune modulation; inflammation; neuroprotection
MAD1L1	7	No	–	–	Cell cycle checkpoint; neuronal cell regulation
MOSPD1	X	No	–	–	Structural differentiation regulator
NHIP	22	No	–	–	Hypomethylated at ASD-associated 22q13.33 locus; placental and brain lower expression; ASD severity correlation
NKX2–5	5	No	–	–	Transcription factor; heart development; placenta-expressed
NOS1AP	1	No	–	–	Synaptic/cytoskeleton transduction; AI-designed placental CpG
NRN1	6	No	–	–	Neuronal growth and synaptic plasticity
PLAGL1	6	No	–	–	Imprinted gene; growth regulator
PVRIG	7	No	–	–	Immune checkpoint regulation
RAB5A	17	No	–	–	Endocytosis; exosome release
RPS6KA2	6	Yes	2	Strong candidate	MAPK signaling; role in cell growth and differentiation
STAT2	12	No	–	–	Interferon signaling; antiviral immune response
TMEM167A	5	No	–	–	Golgi and secretory pathway regulation
ZNF217	20	No	–	–	AI-identified biomarker with predictive value; role in transcription
ZNF267	16	No	–	–	Transcription regulation; zinc finger domain
ZNF385D	3	No	–	–	Neural development; language function
ZNF618	9	No	–	–	Transcription/chromatin interaction

SFARI Score Legend: S = Syndromic; 1 = High confidence; 2 = Strong candidate; 3 = Suggestive evidence; 4–6 = Minimal to no evidence

leading to persistent neuroarchitectural deviations. This temporal dimension helps explain how similar placental disturbances might contribute to diverse outcomes, from childhood-onset ASD to adolescent- or adult-onset psychiatric disorders, depending on when and how developmental trajectories are altered.

4.1. Placental molecular alterations and disrupted neurodevelopment in ASD and SCZ

A mechanistic framework is beginning to take shape when integrating placental OMICS data with known alterations in ASD and SCZ. OMICS alterations in ASD and SCZ placentas converge on evolutionarily conserved pathways involved in oxidative stress responses, immune activation, metabolism, and growth signaling. Notably, these same pathways are highly responsive to prenatal environmental insults, suggesting that OMICS-based signatures may reflect molecular imprinting by in utero stressors. These converging lines of evidence support a model in which placental dysfunction contributes to altered neurodevelopmental trajectories, from early cortical organization through to adult brain structure. This perspective is in line with neuropathological evidence from postmortem studies, which reveal specific cortical alterations consistent with disrupted neurodevelopmental trajectories. For instance, postmortem studies in ASD have revealed focal cortical dysplasias and disorganized cortical laminae in prefrontal regions (Stoner et al., 2014), an excess of excitatory neurons in dorsolateral prefrontal cortex (dlPFC) (Courchesne et al., 2011), and increased dendritic spine density in pyramidal neurons of the prefrontal cortex (Tang et al., 2014). Similarly, in SCZ, histopathological analyses show abnormal minicolumn spacing (Chance et al., 2008), disrupted migration of GABAergic interneurons (Curley et al., 2011), and reduced synaptic connectivity, as evidenced by decreased dendritic spine density on layer III pyramidal neurons in the dlPFC (Glantz and Lewis, 2000).

Supporting these adult brain findings, studies of human fetal brains reveal mechanisms underlying these neuroarchitectural abnormalities.

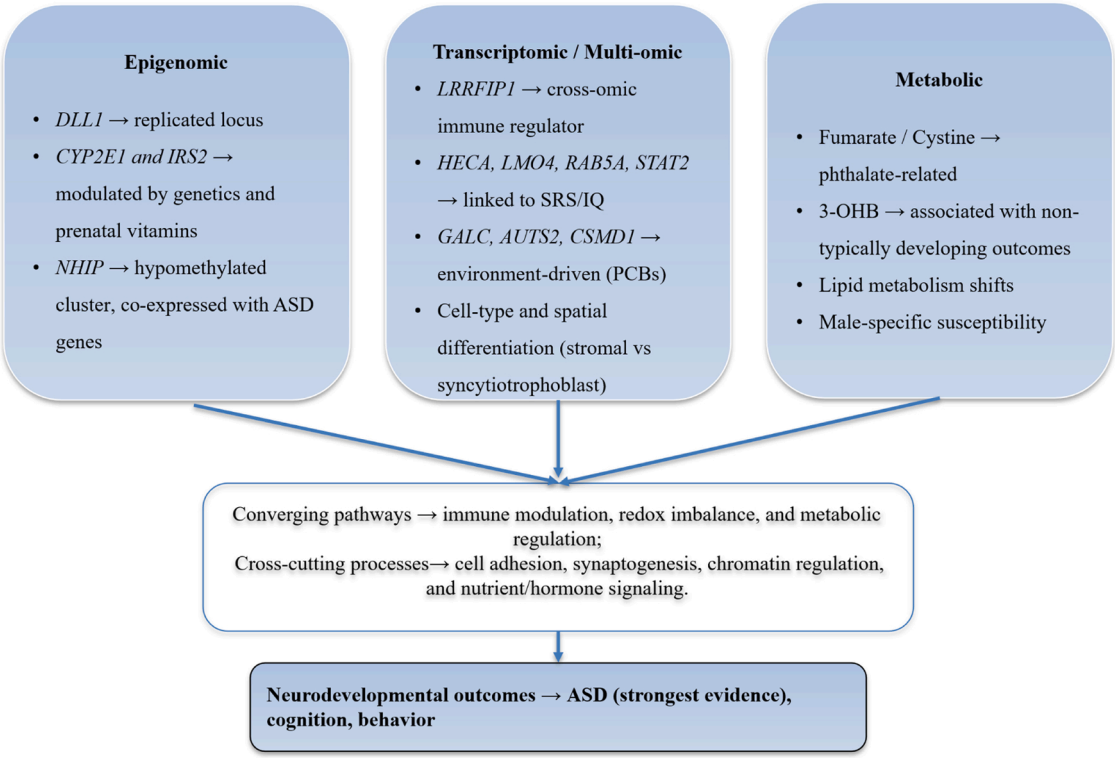

Fig. 2. Convergent pathways from placental omics to neurodevelopmental outcomes. Epigenomic, transcriptomic, and metabolomic studies of placenta-child cohorts identify distinct molecular markers. The figure summarizes main convergent pathways: immune signaling, oxidative stress, and metabolic regulation; and highlights recurrent molecular processes such as cell adhesion, synaptogenesis, chromatin regulation, and nutrient/hormone signaling. Together, these alterations prospectively predict child neurodevelopmental outcomes, with the strongest evidence for autism spectrum disorder (ASD), as well as cognitive and behavioral variation.

Single-nuclei RNA sequencing of prenatal brain tissue indicates that genetic risk variants for SCZ are enriched in developing excitatory neurons and interneurons during mid-gestation, suggesting altered neurogenesis and migration underlying the adult interneuron abnormalities (Cameron et al., 2023). In ASD, research on fetal excitatory neuron populations shows alterations in gene expression and differentiation, providing a developmental basis for the excess excitatory neurons and cortical disorganization seen postmortem (Nowakowski et al., 2017). This is further supported by earlier transcriptomic co-expression analyses implicating midfetal deep-layer cortical projection neurons as a convergence point for ASD risk genes, suggesting temporally and spatially specific vulnerability during cortical circuit formation (Willsey et al., 2013). Furthermore, somatic mutations enriched in regulatory regions active during fetal brain development have been identified in prenatal tissue related to SCZ risk (An and Kim, 2024).

These early neuroarchitectural abnormalities likely arise from disruptions in molecular guidance cues, such as netrins, semaphorins, and chemoattractants like CCL2 (MCP-1) (Bajetto et al., 2002), alongside placental environmental factors, including hypoxia and inflammation, which reprogram genes implicated in neurodevelopmental alterations. These genes, in turn, may influence key developmental signaling pathways, such as IGF2, Wnt, and Notch, that are essential for radial glia function and cortical neurogenesis, thereby linking placental conditions to altered fetal brain development (Gordon et al., 2009; Louvi and Artavanis-Tsakonas, 2006; Luo et al., 2022; Pringle et al., 2010; Wu et al., 2020). This integrative view suggests that placental dysfunction may alter fetal brain wiring by interfering with conserved signaling pathways central to cortical growth.

4.2. Redox pathways

A critical component of placental environment is the regulation of reactive oxygen species (ROS), which play dual roles during gestation. Under physiological conditions, ROS modulate trophoblast differentiation, angiogenesis, and vascular remodeling; however, excessive ROS generation, often driven by hypoxia and inflammation, can impair placental integrity and alter redox-sensitive signaling pathways such as MAPK and NF-κB (Myatt and Cui, 2004; Pereira et al., 2015). Notably, ROS also act as direct signaling molecules in neuronal migration, influencing cytoskeletal dynamics and key migration-related pathways (Bittle et al., 2019; Le Belle et al., 2011; Wilson and González-Billault, 2015). For instance, semaphorin-3 F expression is significantly reduced in preeclamptic placentas, suggesting that hypoxia-driven redox imbalance perturbs guidance cue availability and spatial gradients (as seen in models of placental ischemia) (Stallone et al., 2017).

Placental omics studies have identified several genes central to redox homeostasis that are dysregulated in ASD, implicating oxidative stress as a key mechanism. These include *NHIP* (a hypoxia-responsive gene involved in antioxidant defense) and *CYP2E1* (a ROS-generating enzyme), alongside other candidates such as *AFAP1L2* and *ATP2B1* which link redox balance to cytoskeletal dynamics and calcium signaling, respectively (for detailed gene functions see Tables 1–2) (Bahado-Singh et al., 2021; Santos et al., 2020; Zhu et al., 2019). Variants in *ATP2B1* have also been associated with neurodevelopmental delay and ASD (Rahimi et al., 2022; Santos et al., 2020; Yap et al., 2023). The downregulation of *NHIP*, observed in both ASD placentas and brains, weakens antioxidant defenses during critical developmental windows and disrupts the transcription of neurodevelopmental regulators like *FOXG1* and *NR3C2* (Zhu et al., 2022). Such shifts in the placental redox environment likely impair molecular guidance mechanisms, jeopardizing neuronal migration and cortical organization. In this way, placental oxidative imbalance directly reshapes the intrauterine milieu, altering the molecular cues available to the developing brain. Taken together, these findings point to redox imbalance as a unifying

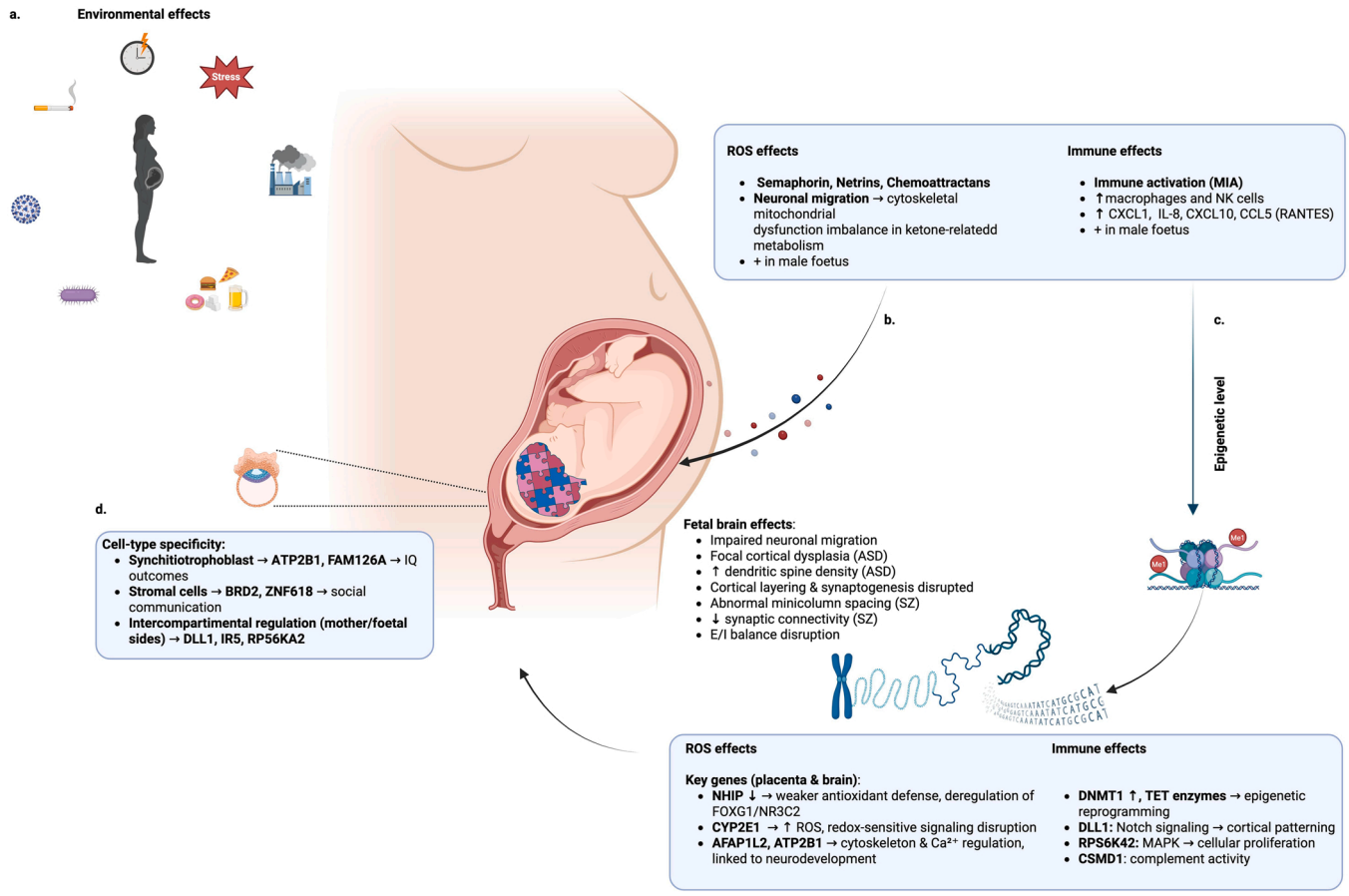

Fig. 3. Integrative pathways linking placental molecular alterations to fetal brain development. a) Environmental effects: Maternal exposures such as endocrine-disrupting chemicals, pollutants, or nutritional imbalances perturb placental molecular programs. These stressors converge on redox balance, immune signaling, and epigenetic regulation, with sex-specific vulnerabilities (notably in male fetuses). b) Direct ROS and immune effects on the fetal brain: Placental oxidative stress and maternal immune activation (MIA) alter neuronal migration, cortical layering, and early synaptic organization through disrupted cytokine signaling (e.g., CXCL1, IL-8, CXCL10, CCL5) and ROS-mediated cytoskeletal dysfunction. These effects directly interfere with cortical circuit formation. c) Indirect epigenetic effects: ROS and inflammatory signaling also reprogram placental epigenetic machinery (e.g., DNMT1, TET enzymes) and immune-sensitive loci (*DLL1, RPS6KA2, CSMD1*). Such persistent alterations reshape placental gene expression and metabolic regulation, indirectly modulating the fetal developmental milieu. d) Cell-type and compartmental specificity: Distinct placental compartments and cell types may contribute differentially to neurodevelopmental risk. For example, syncytiotrophoblast-enriched genes (e.g., *ATP2B1, FAM126A*) have been associated with cognitive outcomes, whereas stromal-enriched genes (e.g., *BRD2, ZNF618*) show links with social functioning in exploratory analyses. Cross-compartmental regulation between maternal and fetal sides (e.g., *DLL1, IRS2, RPS6KA2*) further suggests that spatial context could influence how placental signals are transduced to the fetus.

pathway through which placental dysfunction can translate environmental stress into long-lasting neurodevelopmental risk.

4.3. Immune activation

Just as redox signaling represents a finely balanced system in placental physiology, immune activity at the maternal-fetal interface also plays a dual role in gestation. While tightly regulated immune signals are essential for placental development and maternal-fetal tolerance, excessive or chronic immune activation can disrupt this balance. A key link is MIA, which not only alters cytokine networks but also interferes with hormonal and growth factor pathways essential for fetal neurodevelopment. Importantly, cytokines and immune mediators induced by MIA drive neuronal migration, synaptic maturation, and microglial activation, thereby shaping cortical circuit formation and neuroimmune interactions during critical developmental windows (Deverman and Patterson, 2009; Stumm et al., 2003; Tiveron et al., 2006). MIA simultaneously activates decidual macrophages and uterine NK cells (uNK), increasing CD69^{+} immune populations at the maternal-fetal interface (Fei et al., 2025). By secreting chemokines such as CXCL12 (SDF-1), IL-8, CXCL10, and CCL5 (RANTES), these cells reshape the local chemoattractant landscape at the maternal-fetal interface (Hanna et al., 2006). Given that CXCL12-CXCR4 signaling plays a well-established role in directing neuronal migration in the developing brain, dysregulated placental chemokine expression following MIA may disrupt these guidance cues, either via altered signaling gradients or through secondary effects on epigenetic modulators that influence neurodevelopment (Stumm et al., 2003; Tiveron et al., 2006). Consistent with this, our review identified robust evidence of epigenetic reprogramming in neurodevelopmental and immune-related placental genes. This supports a model in which acute immune signaling and sustained epigenetic changes converge, generating a placental environment that predisposes to neurodevelopmental dysfunction.

Specifically, MIA triggers epigenetic reprogramming in the placenta via altered activity of DNA methyltransferase 1 (DNMT1) and ten-eleven translocation (TET) enzymes, a process likely mediated through IL-6/JAK/STAT3 signaling. Increased DNMT1 expression in the placenta has been observed in inflammatory models, such as following lipopolysaccharide (LPS) exposure (Núñez Estevez et al., 2020), while IL-6 has been shown to promote DNMT1 stabilization and TET3 regulation in other systems (Kong et al., 2019). Furthermore, cord blood levels of pro-inflammatory cytokines correlate with differential methylation at specific placental loci (van Otterdijk et al., 2024), highlighting the direct

impact of prenatal inflammation on the placental epigenome.

Our review identifies a subset of immune-sensitive placental genes, many with established SFARI scores, whose epigenetic regulation may be disrupted by MIA, ultimately influencing fetal neurodevelopment (Tables 1–2). This group includes:

- Notch signaling components like *DLL1* (SFARI Score 2), a consistently replicated locus whose expression is inducible through TLR4 and IL-6/STAT3 signaling, linking MIA directly to its epigenetic dysregulation and potential impairment of cortical patterning (Hildebrand et al., 2018; Schroeder et al., 2016; Suzuki et al., 2018; Zhu et al., 2019).
- MAPK pathway effectors like *RPS6KA2* (SFARI Score 2), which shows epigenetic sensitivity to IL-6 exposure (Bahado-Singh et al., 2022; Balakrishnan et al., 2018; Fischer et al., 2009; Takata et al., 2020). This cytokine-driven epigenetic modulation is mediated by DNMT1 and DNMT3B, providing direct mechanistic evidence linking inflammatory signaling to methylation changes in ASD-relevant placental genes.
- Additional SFARI genes including *AUTS2* (Score 1) (Mouat et al., 2023; Pang et al., 2021, *AGAP1* (Score 2) (Bahado-Singh et al., 2022; Lewis et al., 2023) and *CSMD1* (Score 2) (Baum et al., 2024; Mouat et al., 2023), which further connect placental dysfunction to processes like neuronal migration (*AUTS2*), synaptic organization (*AGAP1*), and neuroimmune interactions (*CSMD1*). While direct evidence of cytokine-driven changes for these specific genes is still emerging, their known functions position them within broader networks of placental immune signaling.

This collective evidence positions placental immune signaling as both an acute disruptor and a long-term epigenetic modifier of fetal neurodevelopment.

Experimental models further support a causal link between placental dysfunction and neurodevelopmental disorganization. In rodents, MIA-induced IL-6 elevation leads to microglial priming, altered cortical thickness, and social deficits in offspring (Choi et al., 2016; Estes and McAllister, 2016). Knockout of Igf2 or inhibition of PI3K/mTOR signaling in trophoblasts impairs nutrient transfer and fetal brain growth (Sferruzzi-Perri and Camm, 2016). Similarly, maternal oxidative stress induces synaptic and behavioral abnormalities resembling ASD (Sun et al., 2025). Although genes such as *CYP2E1*, *IRS2*, *NHIP*, *AUTS2*, *AGAP1*, and *RPS6KA2* have been studied in various biological contexts, including neuronal function and metabolism, their specific roles in placental function during MIA or oxidative stress remain underexplored in targeted animal models. Future work dissecting these genes in experimental MIA or oxidative stress paradigms represents a crucial next step to bridge placental gene dysregulation with altered neurodevelopmental trajectories.

In summary, MIA acts both as an acute disruptor, altering chemokine and cytokine gradients, and as a chronic modifier, reshaping placental epigenetic programs in ASD-relevant genes. This dual role underscores immune activation as a central driver of lasting neurodevelopmental risk.

4.4. Metabolic signaling in the placenta and its role in fetal brain development

Placental metabolism plays a fundamental role in supporting fetal brain development, particularly during periods of intense neurogenesis and synaptogenesis, by delivering essential substrates such as ketone bodies, amino acids, and lipids (Bowman et al., 2020). Disruptions in these metabolic pathways can alter not only the quantity but also the balance of these substrates, with potential consequences for myelination, neurotransmitter synthesis, and the maturation of neural circuits.

Two studies identified in our systematic review (Parenti et al., 2024, 2022) pointed to such metabolic alterations, involving fumarate, cystine, uridine, and ketone-related metabolites like 3-OHB. Although associations remained nominal after correction, the biological relevance of these metabolites, particularly their convergence on mitochondrial function, redox balance, and lipid metabolism, suggests that placental adaptability may be impaired in fetuses later showing atypical neurodevelopment.

Mechanistically, these findings converge on two interconnected levels of dysfunction. The first involves mitochondrial and substrate metabolism. Altered levels of tricarboxylic acid (TCA) cycle intermediates (e.g., fumarate) and amino acids (e.g., cystine) may reflect broader mitochondrial stress. Ketone bodies such as 3-OHB function not only as energy substrates but also as signaling molecules that enhance antioxidant responses (e.g., via NRF2 activation) and modulate inflammation (Izuta et al., 2017; Youm et al., 2015). While these shifts may initially represent adaptive responses to oxidative stress, their persistence may signal a state of metabolic insufficiency, with potential consequences for neural development.

The second level of dysfunction involves nutrient-sensing and hormonal signaling pathways. The mechanistic target of rapamycin (mTOR), a key nutrient sensor in placental trophoblasts, is highly sensitive to environmental stressors such as hypoxia and nutrient deprivation (Jansson et al., 2012). When dysregulated, mTOR signaling reduces the placenta's capacity to import amino acids and lipids, essential building blocks for brain development, and has been linked to alterations in dendritic spine density and excitatory neuron populations observed in ASD and SCZ (Costa-Mattioli and Monteggia, 2013; Courchesne et al., 2011). In parallel, hormonal signaling cascades, particularly the growth hormone-insulin-like growth factor (GH-IGF) axis, are vulnerable to disruption by inflammatory stimuli. In animal models, maternal IL-6 activates the IL-6Rα/gp130/STAT3 pathway in placental spongiotrophoblasts, leading to SOCS3 induction and suppression of the GH–IGF axis (Hsiao and Patterson, 2011), a mechanism known to impair neurogenesis, synaptogenesis, and myelination (Gubbi et al., 2018). This pathway is further modulated by epigenetic mechanisms: *IRS2*, a key intracellular effector of IGF-1 signaling, was found differentially methylated in placentas of children later diagnosed with ASD, independent of genotype but influenced by maternal prenatal vitamin intake (Zhu et al., 2019). Given its role in mediating IGF-1-driven cell proliferation and differentiation (Machado-Neto et al., 2018), dysregulation of *IRS2* could amplify the effects of maternal inflammation on fetal brain development.

Together, these metabolic and signaling disturbances, rooted in mitochondrial dysfunction, redox imbalance, hormonal disruption, and epigenetic regulation, may compromise placental efficiency and impair the delivery of neurotrophic support to the fetus. These mechanisms offer a biological framework linking early placental alterations to later neurodevelopmental vulnerability, consistent with the candidate metabolomic markers identified in our review.

4.5. Cell-type and spatially resolved placental signatures: implications for neurodevelopment

The placenta is a highly heterogeneous organ composed of specialized cell types that collectively orchestrate fetal development and mediate maternal-fetal exchange. This cellular and spatial complexity introduces a critical dimension for interpreting how molecular alterations in the placenta may influence neurodevelopmental trajectories. Trophoblast subtypes (e.g., cytotrophoblasts, syncytiotrophoblasts), endothelial cells, and Hofbauer cells (placental macrophages) each express distinct transcriptional and epigenetic programs, some of which intersect with neurodevelopmental disorder–associated loci (Bakulski et al., 2021; Santos et al., 2020).

Evidence from placenta-child matched studies is especially compelling. Santos et al. (Santos et al., 2020) identified trophoblast and stroma specific gene expression patterns associated with later child cognitive and social functioning. For example, *ATP2B1* and *FAM126A*,

(syncytiotrophoblast-enriched) were linked to IQ, while *BRD2* and *ZNF618* (stroma-enriched) were associated with social responsiveness. Although none of these genes are currently included in the SFARI database, their functions, respectively in calcium transport, myelination, chromatin remodeling, and transcription regulation, are highly relevant to neurodevelopment.

Similarly, Bakulski et al., reported that while no CpG reached genome-wide significance, nominally associated sites were enriched for SFARI genes, with moderate correlations across maternal and fetal placental compartments, suggesting inter-compartmental regulation. This cross-compartmental regulation is particularly relevant for genes such as *DLL1*, *IRS2*, and *RPS6KA2*, whose expression reflects both maternal and fetal signaling inputs (Bakulski et al., 2021).

In parallel, cross-sectional mapping studies offer complementary but indirect insights. Ursini et al. prioritized 139 placenta-specific SCZ risk genes, with sex-biased expression patterns (Ursini et al., 2023). Single-cell data localized down-regulated risk genes to syncytiotrophoblasts and up-regulated genes to villous/extravillous trophoblasts and Hofbauer cells, particularly in male placentas. Other spatially resolved datasets (Ursini et al., 2021, 2018) further support the concept of functional placental microdomains, e.g., nutrient sensing in trophoblasts versus immune surveillance in Hofbauer cells.

Hofbauer cells also emerge as key players in placental-brain crosstalk. These fetal macrophages dynamically respond to MIA and may transmit inflammatory signals to the fetus by releasing cytokines that prime fetal microglia and influence synaptic pruning (Batorsky et al., 2024; Pavlov et al., 2020). Although psychiatric risk gene enrichment has not been directly demonstrated in Hofbauer cells, their immunomodulatory role situates them within the immune-synaptic pathways discussed in Section 4.3.

Taken together, matched-outcome studies provide the strongest evidence of placental molecular signatures predicting child neurodevelopment, while cross-sectional mapping highlights broader cell-type- and compartment-specific vulnerability windows. Importantly, maternal and fetal compartments show coordinated yet distinct molecular regulation, with cross-compartmental signatures emerging as particularly relevant for psychiatric risk. Within this landscape, trophoblasts act as central hubs for nutrient and hormone sensing, whereas Hofbauer cells mediate immune signaling, together shaping pathways that impact the developing brain. From a clinical perspective, matched designs are especially informative for establishing predictive value, while spatial mapping refines the search for cellular targets that may serve as biomarkers or intervention points in the future.

4.6. Sex-specific placental signatures and neurodevelopmental risk

Sex-fetus differences in placental responses to environmental stressors are emerging as a critical moderator of neurodevelopmental outcomes, offering insight into why males exhibit higher susceptibility to disorders such as ASD and SCZ (Gadow, 2013; Loomes et al., 2017). Placental profiles differ markedly by fetal sex, with male-associated placentas showing greater inflammatory, oxidative, and metabolic dysregulation under prenatal stress, potentially underpinning sex-specific neurodevelopmental vulnerabilities. Placentas from male fetuses exhibit stronger pro-inflammatory responses to immune challenges. Research in rodent models of MIA shows that male-associated placentas produce significantly higher levels of cytokines, including IL-6, TNF-α, and CXCL1 following exposure to poly(I:C) or LPS (Braun et al., 2019; Osman et al., 2024). This exaggerated male inflammatory response is attenuated by maternal anti-inflammatory treatment, indicating that sex-biased placental reactivity is at least partially modifiable (Bronson and Bale, 2014).

Such differential inflammatory reactivity coincides with sex-biased activation of oxidative and metabolic pathways. In particular, prenatal stressors, including maternal psychological stress, have been shown to induce male-specific upregulation of hypoxia-inducible factor 3 subunit alpha (HIF3A) in the placenta, suggesting heightened hypoxic sensitivity in males compared to females (Cowell et al., 2020). These sex differences converge with human data showing increased placental activity of nuclear factor kappa-light-chain-enhancer of activated B cells subunit p65 (NF-κB p65) in male fetuses from preeclamptic pregnancies. NF-κB p65 is a key transcription factor involved in the regulation of inflammation, oxidative stress responses, trophoblast apoptosis, and mitochondrial dysfunction (Armistead et al., 2020; Mansell et al., 2019). Conversely, the female placenta demonstrates greater transcriptional adaptability, with upregulation of epigenetic regulators like O-linked N-acetylglucosamine transferase (OGT) and enhanced expression of stress-response genes, which confer resilience by buffering inflammatory and metabolic dysregulation (Nugent et al., 2018). These findings suggest an inherent sex-specific vulnerability at the maternal–fetal interface.

Consistent with these mechanisms, results from our review further support this perspective. Notably, prenatal phthalate exposure was associated with significant reductions in placental metabolite levels, specifically carnitine, O-acetylcarnitine, glucitol, and N-acetylneuraminate, key molecules involved in lipid metabolism and cellular homeostasis. Crucially, the overall placental metabolome was associated with neurodevelopmental outcomes only in male offspring, suggesting sex-dependent metabolic sensitivity, although single-metabolite effects did not survive multiple testing correction (Parenti et al., 2022). Moreover, Zhu et al., identified male-specific epigenetic modifications in placental genes such as *CYP2E1* and *IRS2*, (Zhu et al., 2019). The convergence of metabolomic shifts and epigenetic alterations in male placentas underscores a combined pathway of increased vulnerability.

Together, these findings highlight sex-specific patterns of placental programming, marked by greater inflammatory and oxidative vulnerability in male fetuses, coupled with reduced engagement of protective metabolic and transcriptional pathways. This combination may contribute to sex differences in neurodevelopmental trajectories by disrupting placental regulation of nutrient delivery and oxidative homeostasis, key processes for healthy fetal brain development. Such mechanisms offer a plausible biological basis for the higher prevalence of neurodevelopmental disorders among males.

4.7. Maternal circadian rhythm as a temporal integrator of placental and fetal responses?

While these molecular disruptions offer a mechanistic framework, a critical question remains: what orchestrates their temporal emergence and specificity across gestation? The diverse epigenetic and transcriptional alterations identified here, represent isolated molecular footprints of environmental insults, or are they coordinated by higher-order maternal-fetal physiological systems that could regulate fetal development over time? Here, we outline a hypothetical framework, emerging as a theoretical extension of the studies we reviewed, which should be interpreted as a forward-looking perspective rather than a definitive conclusion. Within this framework, we consider the possibility that maternal circadian rhythms function as higher-order temporal coordinators of placental and fetal processes.

In the complex physiological environment of pregnancy, some coordination across systems must occur to meet the evolving needs of the fetus. Circadian biology offers one potential integrative mechanism. Maternal biological rhythms, particularly circadian cycles, may play a central role in coordinating the timing of key physiological processes during pregnancy. Influenced by environmental cues such as light exposure and sleep-wake cycles, these rhythms could provide an integrative temporal framework that aligns immune, metabolic, redox and neurodevelopmental pathways with critical stages of placental and fetal development.

Circadian rhythms regulate nearly all biological systems: immune responses vary by time of day; metabolic pathways follow feeding-fasting cycles; redox balance responds to light-dark transitions; and

hormone secretion is tightly circadian (Méndez et al., 2016; Myung et al., 2025). These rhythms are generated by central and peripheral clocks and the placenta itself expresses core clock genes, including *BMAL1*, *CLOCK*, *PER2*, and *CRY1* (Waddell et al., 2012). Moreover, maternal melatonin crosses the placenta and binds to MT1/MT2 receptors, thereby influencing placental physiology (Joseph et al., 2024).

Although no longitudinal study directly implicated canonical clock genes, several loci identified in placental omics are circadian-regulated (Table S3), suggesting maternal rhythms may modulate their placental expression. For instance, *DLL1*, shows oscillatory expression during embryonic somitogenesis and in muscle stem cells, where it regulates the balance between differentiation and renewal. This rhythmicity suggests time-sensitive regulation potentially responsive to maternal temporal cues (Bone et al., 2014; Zhang et al., 2021). Similarly, *CYP2E1* is under strong circadian control in the liver via clock proteins such as PER1, raising the possibility that its placental expression could also vary with maternal circadian rhythms, particularly under metabolic or environmental stress (Ge et al., 2021). *RPS6KA2* shows epigenetic sensitivity to night-shift work and chronotype in humans, implying that maternal circadian disruption could influence its regulation during pregnancy (Adams et al., 2017). Further, genes such as *IRS2* shows direct circadian responsiveness; in mice, blue-light suppression at night restores hepatic *IRS2* expression, underscoring its light-sensitive regulation (Nagai et al., 2019).

Additional loci with circadian regulation are listed in Supplementary Table S3, including genes involved in GABAergic signaling (e.g., *GABBR1*), melatonin-sensitive pathways (e.g., *GPR135*) (Albers et al., 2017; Liu et al., 2025; Oishi et al., 2017), and cardiac or vesicular regulation (e.g., *NKX2–5, RAB5A*) (Xie et al., 2019; Zhang and Wei, 2021). Collectively, these patterns reinforce the plausibility of a circadian layer of regulation in the placenta. This motivates what we tentatively term a *circadian-epigenetic gating model*, in which maternal rhythms might modulate the timing of placental susceptibility to environmental perturbations. The core circadian transcription factor *BMAL1* (*ARNTL*), along with other clock genes, represents a key molecular candidate for mediating the influence of external cues on downstream placental alterations and, ultimately, fetal brain development. *BMAL1* regulates daily fluctuations in inflammatory monocytes and coordinates immune and metabolic rhythms (Nguyen et al., 2013). In animal models, the severity of viral infections such as herpes and influenza depends critically on the time of day when infection occurs, with infections initiated at the onset of the active phase causing more severe disease; this time-of-day effect is abolished in *BMAL1* knockout mice, underscoring its central role (Edgar et al., 2016). This circadian gating of immune activity suggests that the timing of environmental insults, rather than their mere presence, could shape placental and fetal responses. In line with this, leukocyte migration into tissues peaks during the maternal active phase, which may correspond to a window of increased vulnerability to pathogens, whereas inflammatory cytokine release and oxidative stress responses peak during the rest phase, possibly amplifying placental immune activation when insults occur during this time frame (Besedovsky et al., 2011; Scheiermann et al., 2013). Complementary evidence from human studies shows that morning vaccinations elicit stronger antibody responses compared to those administered in the afternoon, further underscoring the diurnal modulation of immune competence (Long et al., 2016). While these findings do not establish a causal link to placental processes, they highlight *BMAL1* and other maternal clock genes as a plausible gatekeeper of temporal vulnerability.

Maternal melatonin further conveys time-of-day information to the placenta and fetus. Melatonin is secreted predominantly during the maternal dark phase. Importantly, melatonin crosses the placenta, binding to MT1 and MT2 receptors expressed in both trophoblasts and fetal tissues, where it entrains circadian gene expression, enhances antioxidant defenses, and modulates immune and redox signaling (Joseph et al., 2024; Voiculescu et al., 2014). This rhythmic transfer raises the possibility that the placenta and fetus receive greater melatonin-mediated protection during the maternal rest phase, precisely when inflammatory cytokine production and oxidative stress responses naturally peak (Besedovsky et al., 2011). In this context, melatonin may act as a temporal shield, buffering the placenta and fetal brain from nocturnal inflammatory or metabolic insults. Conversely, disruption of maternal melatonin rhythms, for example due to night-time light exposure or circadian misalignment, may reduce this protection, although direct evidence in humans remains limited. Human data provide preliminary support for this framework. Maternal circadian disruption, caused by factors such as shift work, jet travel across time zones, mistimed eating, and excessive artificial light exposure at night, has been linked to alterations in placental DNA methylation patterns (Clarkson-Townsend et al., 2021) as well as increased risks of psychiatric disorders in offspring, including depression and anxiety (Hoyniak et al., 2024; Kember et al., 2023; Strohmaier et al., 2019). While altered placental methylation associated with maternal circadian disruption has been observed, the direct causal pathways linking these epigenetic changes to neurodevelopmental and mental health outcomes in offspring remain to be established. Notably, Hoyniak et al., provided evidence that disrupted sleep and circadian rhythms during pregnancy, especially when compounded by social disadvantage, are associated with reductions in neonatal cortical gray and white matter volumes, as well as smaller cortical surface areas and subcortical gray matter volumes (Hoyniak et al., 2024). Although these associations are correlative, they resonate with the neuropathological evidence described in Section 4.1, which highlights cortical disorganization, altered neuron populations, and disrupted synaptic architecture observed in postmortem studies of ASD and SCZ. Moreover, they are consistent with neuroimaging studies demonstrating that changes in cortical white-gray matter contrast predict ASD diagnosis and severity (Bezgin et al., 2018), and that reduced white matter integrity correlates with cortico-subcortical gray matter deficits in SCZ (Miyata et al., 2009).

Maternal circadian rhythms could therefore shape how the placenta responds to environmental insults across gestational stages, thereby influencing fetal brain development. While the nature of environmental insults, such as inflammation, metabolic stress, or endocrine disruption, may remain relatively constant throughout pregnancy, the subset of placental genes responsive to circadian cues likely shifts depending on developmental timing, altering downstream effects on the fetal brain.

During early to mid-gestation (approximately weeks 8–24), cortical development is dominated by neurogenesis, neuronal migration, and interneuron positioning. In this window, placental expression of circadian-sensitive genes such as *DLL1*, *CYP2E1*, *RPS6KA2*, *GABBR1*, *GATS*, and *GPR135* may play a key role in shaping early brain architecture. Dysregulation of these genes, could interfere with neurodevelopmental programs underlying ASD or ADHD, conditions increasingly associated with early gestational perturbations (Love et al., 2024). In late gestation (from week 25 onward), when synaptogenesis, axonal maturation, and pruning become central, a different set of circadian-modulated genes, such as *IRS2*, *NKX2–5*, *RAB5A*, and *STAT2*, may shape placental contributions to synaptic stability and circuit refinement. Misregulation of these genes under conditions of circadian misalignment could impair plasticity and disrupt the excitation/inhibition (E/I) balance, a neurobiological feature commonly implicated in both ASD and SCZ (Canitano and Pallagrosi, 2017). However, while E/I imbalance may be a shared downstream consequence, its developmental origins likely differ: early alterations may affect excitatory lineage expansion or interneuron placement, while late gestation overlaps with critical windows of synaptogenesis and microglia-mediated synaptic pruning, making this timeframe particularly vulnerable to disruptions that could compromise circuit refinement and contribute to SCZ pathogenesis (Eltokhi et al., 2020).

This model remains speculative but generates testable hypotheses. Future research should include longitudinal tracking of maternal circadian markers (e.g., melatonin) and maternal-fetal circadian

genotyping. Linking these with neuroimaging and behavioral data in offspring could clarify how placental signatures relate to circuit-level and clinical outcomes. If supported, such evidence might inform timing-specific interventions, such as optimizing maternal sleep hygiene or melatonin supplementation, tailored to chronotype and fetal risk. Ultimately, while not yet empirically validated, restoring maternal circadian alignment during critical gestational windows may represent a promising pathway to reduce long-term neurodevelopmental vulnerability.

In summary, maternal circadian rhythms may act as higher-order temporal integrators of placental physiology, gating the impact of environmental insults across gestation. This forward-looking framework provides a testable link between maternal rhythms, placental signatures, and long-term neurodevelopmental outcomes.

4.8. Clinical implications, preventive strategies, and translational opportunities

The synthesis of longitudinal placental studies underscores several translational opportunities with direct clinical relevance (Table 3).

A first and particularly promising direction concerns the development of placental molecular signatures as early biomarkers of neurodevelopmental risk. DNA methylation changes, transcriptomic alterations, and metabolomic shifts identified in relation to maternal exposures suggest that the placenta is not only a mediator of fetal development but also a measurable indicator of adverse intrauterine conditions. Such signatures can already be assessed postnatally through the analysis of cord blood or placental tissue. However, the field is rapidly advancing toward prenatal, non-invasive strategies. In this regard, maternal blood provides access to several placental-derived signals. Extracellular vesicles (EVs), which carry miRNAs and proteins reflecting placental state, have already been shown to predict complications such as preeclampsia with clinically useful sensitivity (Ghosh et al., 2024). Similarly, cell-free fetal DNA (cffDNA), a well-established tool for chromosomal screening, originates primarily from placental trophoblasts and could be expanded to assess epigenetic or transcriptional profiles linked to neurodevelopmental outcomes (Yuen et al., 2024). In parallel, maternal inflammatory and metabolic profiles are increasingly recognized as dynamic markers of intrauterine physiology and have been associated with child neurodevelopmental trajectories in prospective cohorts (Parenti et al., 2024). Together, these approaches suggest that a non-invasive biomarker-based risk stratification for psychiatric vulnerability may be feasible in the foreseeable future.

Beyond biomarker discovery, our findings highlight that placental molecular alterations often reflect modifiable maternal factors. Prenatal immune activation, oxidative imbalance, metabolic disruption, and exposure to environmental toxicants such as phthalates or air pollutants consistently leave molecular footprints in the placenta. This provides a rationale for preventive strategies aimed at optimizing maternal health during pregnancy, through nutritional interventions, management of chronic inflammation or metabolic dysregulation, and reduction of toxicant exposure. Importantly, many of these pathways are already targeted in the context of other obstetric conditions, such as preeclampsia or intrauterine growth restriction, suggesting that lessons from these clinical domains could inform preventive approaches relevant to neurodevelopmental risk. Targeted public health approaches, such as policies limiting chemical exposure, workplace protections for pregnant individuals, and improved prenatal screening, may further reduce risk at the population level.

Emerging mechanistic insights highlight opportunities for therapeutic translation. Maternal anti-inflammatory strategies, melatonin supplementation or targeted antioxidant interventions are already under investigation in related contexts such as preeclampsia and intrauterine growth restriction (Sebastiani et al., 2022). While direct evidence in relation to psychiatric outcomes is lacking, these interventions exemplify how placental pathways might become actionable therapeutic targets in the future, provided that safety and efficacy are rigorously established.

A critical implication of the reviewed evidence is that developmental timing matters. Placental molecular responses are not static but change across gestation, and in many cases differ by fetal sex. This means that effective interventions will likely need to be carefully timed to periods of heightened vulnerability, and potentially adapted to sex-specific developmental trajectories. Such a temporally and biologically nuanced approach could substantially increase the efficacy of preventive measures while minimizing unintended effects.

Finally, while most implications emerge directly from the longitudinal studies reviewed, it is worth noting a speculative but intriguing extension. Maternal circadian rhythms may function as a higher-order coordinator of placental and fetal responses. If supported by future research, this perspective would imply that maternal circadian health, shaped by sleep, light exposure, and daily activity patterns, might represent an additional, modifiable factor in shaping fetal neurodevelopmental risk. Although preliminary, this line of reasoning opens new avenues for translational exploration, suggesting that lifestyle-based interventions to promote circadian alignment could one day complement molecularly targeted strategies.

Table 3
Clinical Implications and Translational Opportunities in Placental Omics.

Intervention Level	Practical Strategy	Rationale
Biomarker detection	Analyze EVs, cffDNA, maternal metabolic/cytokine profiles. Sample cord blood/placenta at birth	Early identification of risk profiles
Preventive care	Optimize maternal nutrition Reduce exposures Manage inflammation/ oxidative stress	Mitigate placental dysregulation
Translational medicine	Test antioxidants/anti-inflammatories where appropriate	Target mechanistic pathways
Timing-specific strategies	Intervene during critical developmental windows. Consider fetal sex for tailored approaches	Enhance efficacy and reduce adverse outcomes
Lifestyle modulation	Promote circadian alignment (sleep hygiene, light exposure)	Potential temporal regulator of placental vulnerability

EVs – Extracellular Vesicles; cffDNA, Cell-free Fetal DNA;

5. Limits

Some limitations temper our conclusions. First, most studies reviewed are limited to high-risk or preterm cohorts with relatively small sample sizes. Second, almost all longitudinal placental omics studies to date focus on ASD, whereas evidence for SCZ and other psychiatric disorders is indirect, relying on genetic enrichment or extrapolations rather than prospective linkage. This asymmetry limits the generalizability of our conclusions beyond ASD. Third, in the context of adult psychiatric disorders, most findings rely on indirect associations drawn from existing GWAS and placental omics data, rather than from longitudinal studies that follow individuals from birth to clinical outcome. Fourth, current studies insufficiently account for placental cell-type composition and often lack integrative neuroimaging or behavioral data.

In addition to these limitations of the included evidence, certain constraints apply to our review process itself. We limited inclusion to studies published in English, which may have led to the exclusion of relevant findings reported in other languages. Furthermore, our focus on human placental tissue excluded experimental animal and in vitro studies, which might have provided additional mechanistic insights. We also cannot exclude the possibility of publication bias or missed grey

literature. This review was conceptually framed around psychiatric and behavioral outcomes. Future studies may broaden this framework to encompass related neurological domains, such as intellectual disability and movement disorders, to provide a more integrated view of the placenta-brain continuum.

6. Conclusion

This systematic review affirms the placenta's pivotal role as an active mediator and integrator of maternal-fetal signals, encoding a molecular memory of in utero exposures that shapes neurodevelopmental trajectories. Our synthesis converges on several critical messages for the field.

First, longitudinal human studies provide consistent evidence that placental omics signatures, epigenetic, transcriptomic, and metabolic, are prospectively associated with child neurodevelopmental outcomes, particularly ASD. These molecular changes converge on core dysregulated pathways involving immune and inflammatory signaling, oxidative stress responses, and metabolic homeostasis.

Second, a fundamental gap persists: the absence of studies directly linking placental molecular measures to psychiatric outcomes in adolescence or adulthood through one-to-one placenta-offspring linkage. This represents a critical missed opportunity to understand the placental origins of disorders with later clinical onset, such as SCZ.

Third, future research must not only be larger and longer but also smarter. It must account for critical moderators like fetal sex and placental cell-type specificity, and integrate data across molecular, imaging, and clinical levels. Furthermore, our review suggests the need to explore higher-order integrators of placental function, such as the proposed role of maternal circadian rhythms in temporally gating molecular responses to environmental insults. While speculative, this perspective underscores the complexity of the maternal-placental-fetal system and opens new avenues for investigating the timing of risk and resilience.

Finally, the ultimate goal is to translate these insights into clinical actions. This body of work underscores the potential to transform placental research into clinical tools. The development of placental biomarkers for early risk identification and the pursuit of preventive strategies targeting modifiable maternal factors (e.g., nutrition, inflammatory status, environmental toxicants) lay the groundwork for a new paradigm in psychiatry, shifting the focus from treatment in adulthood to pre-symptomatic risk mitigation before birth.

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Riccardo Guglielmo: Conceptualization, Methodology, Data curation, Formal analysis, Investigation, Writing-original draft, Writing-review & editing, Visualization, Project administration. Giulia Sartoris: Literature search, Data curation, Writing-review & editing. Pasquale Striano: Supervision, Writing-review & editing. Valerio Gaetano Vellone: Supervision, Writing-review & editing. Michele Paudice: Validation, Writing-review & editing. Francesca Buffelli: Validation. Giovanni Fiorito: Formal analysis, Data curation, Writing-review & editing. Eralda Myslimi: Risk of bias assessment, Formal analysis, Writing-review & editing. Greta Urti: Literature search, Data curation. Andrea Escelsior: Visualization (figures), Writing-review & editing. Alberto Inuggi: Methodology, Data visualization, Validation. Mario Amore: Supervision, Project administration. Gianluca Serafini: Supervision, Project administration.

Declaration of Competing Interest

The authors have no conflicts of interest to declare.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.neubiorev.2025.106433.

Data availability

No data was used for the research described in the article.

References

Adams, C.D., Jordahl, K.M., Copeland, W., Mirick, D.K., Song, X., Sather, C.L., Kelsey, K., Houseman, A., Davis, S., Randolph, T., Bhatti, P., 2017. Nightshift work, chronotype, and genome-wide DNA methylation in blood. Epigenetics 12, 833–840. https://doi.org/10.1080/15592294.2017.1366407.

Albers, H.E., Walton, J.C., Gamble, K.L., McNeill, J.K., Hummer, D.L., 2017. The dynamics of GABA signaling: revelations from the circadian pacemaker in the suprachiasmatic nucleus. Front Neuroendocr. 44, 35–82. https://doi.org/10.1016/J.YFRNE.2016.11.003.

An, J.Y., Kim, Y., 2024. Genomic patterns in the schizophrenia brain. Science 386, 146–148. https://doi.org/10.1126/SCIENCE.ADS6781/ASSET/F8548743-B7C4-425D-B3D4-5C67B5AB5335/ASSETS/GRAPHIC/SCIENCE.ADS6781-F1.SVG.

Anderson, G.M., Jacobs-Stannard, A., Chawarska, K., Volkmar, F.R., Kliman, H.J., 2007. Placental trophoblast inclusions in autism spectrum disorder. Biol. Psychiatry 61, 487–491. https://doi.org/10.1016/j.biopsych.2006.03.068.

Armistead, B., Kadam, L., Drewlo, S., Kohan-Ghadr, H.R., 2020. The role of NFκB in healthy and preeclamptic placenta: trophoblasts in the spotlight. Int. J. Mol. Sci. 21, 1775. https://doi.org/10.3390/IJMS21051775.

Bahado-Singh, R.O., Vishweswaraiah, S., Aydas, B., Radhakrishna, U., 2021. Placental DNA methylation changes and the early prediction of autism in full-term newborns. PLoS One 16, e0253340. https://doi.org/10.1371/JOURNAL.PONE.0253340.

Bahado-Singh, R.O., Vishweswaraiah, S., Aydas, B., Radhakrishna, U., 2022. Artificial intelligence and placental DNA methylation: newborn prediction and molecular mechanisms of autism in preterm children. J. Matern. Fetal Neonatal Med. 35, 8150–8159. https://doi.org/10.1080/14767058.2021.1963704.

Bajetto, A., Bonavia, R., Barbero, S., Schettini, G., 2002. Characterization of chemokines and their receptors in the central nervous system: physiopathological implications. J. Neurochem. 82, 1311–1329. https://doi.org/10.1046/J.1471-4159.2002.01091.X;PAGE:STRING:ARTICLE/CHAPTER.

Bakulski, K.M., Dou, J.F., Feinberg, J.I., Aung, M.T., Ladd-Acosta, C., Volk, H.E., Newschaffer, C.J., Croen, L.A., Hertz-Picciotto, I., Levy, S.E., Landa, R., Feinberg, A. P., Fallin, M.D., 2021. Autism-Associated DNA methylation at birth from multiple tissues is enriched for autism genes in the early autism risk longitudinal investigation. Front. Mol. Neurosci. 14. https://doi.org/10.3389/FNMOL.2021.775390/PDF.

Balakrishnan, A., Guruprasad, K.P., Satyamoorthy, K., Joshi, M.B., 2018. Interleukin-6 determines protein stabilization of DNA methyltransferases and alters DNA promoter methylation of genes associated with insulin signaling and angiogenesis. Lab. Investig. 98, 1143–1158. https://doi.org/10.1038/S41374-018-0079-7/ATTACHMENT/14312AFA-6BF7-4349-9CCB-42098E177566/MMC1.PDF.

Batorsky, R., Ceasrine, A.M., Shook, L.L., Kislal, S., Bordt, E.A., Devlin, B.A., Perlis, R.H., Slonim, D.K., Bilbo, S.D., Edlow, A.G., 2024. Hofbauer cells and fetal brain microglia share transcriptional profiles and responses to maternal diet-induced obesity. Cell Rep. 43, 114326. https://doi.org/10.1016/J.CELREP.2024.114326.

Baum, M.L., Wilton, D.K., Fox, R.G., Carey, A., Hsu, Y.H.H., Hu, R., Jäntti, H.J., Fahey, J. B., Muthukumar, A.K., Salla, N., Crotty, W., Scott-Hewitt, N., Bien, E., Sabatini, D.A., Lanser, T.B., Frouin, A., Gergits, F., Håvik, B., Gialeli, C., Nacu, E., Lage, K., Blom, A. M., Eggan, K., McCarroll, S.A., Johnson, M.B., Stevens, B., 2024. CSMD1 regulates brain complement activity and circuit development. Brain Behav. Immun. 119, 317–332. https://doi.org/10.1016/j.bbi.2024.03.041.

Besedovsky, L., Lange, T., Born, J., 2011. Sleep and immune function. Pflug. Arch. 463, 121. https://doi.org/10.1007/S00424-011-1044-0.

Bezgin, G., Lewis, J.D., Evans, A.C., 2018. Developmental changes of cortical White–gray contrast as predictors of autism diagnosis and severity. Transl. Psychiatry 8, 1–12. https://doi.org/10.1038/S41398-018-0296-2;SUBJMETA=1373,2423,476,53,692,699;KWRD=AUTISM+SPECTRUM+DISORDERS,PREDICTIVE+MARKERS.

Bittle, J., Menezes, E.C., McCormick, M.L., Spitz, D.R., Dailey, M., Stevens, H.E., 2019. The role of redox dysregulation in the effects of prenatal stress on embryonic interneuron migration. Cereb. Cortex (N. Y. NY) 29, 5116. https://doi.org/10.1093/CERCOR/BHZ052.

Bone, R.A., Bailey, C.S.L., Wiedermann, G., Ferjentsik, Z., Appleton, P.L., Murray, P.J., Maroto, M., Kim Dale, J., 2014. Spatiotemporal oscillations of notch1, Dll1 and NICD are coordinated across the mouse PSM. Development (Cambridge) 141, 4806–4816. https://doi.org/10.1242/DEV.115535/-/DC1.

Bowman, C.E., Arany, Z., Wolfgang, M.J., 2020. Regulation of maternal–fetal metabolic communication. Cell Mol. Life Sci. 78, 1455. https://doi.org/10.1007/S00018-020-03674-W.

Braun, A.E., Carpentier, P.A., Babineau, B.A., Narayan, A.R., Kielhold, M.L., Moon, H.M., Shankar, A., Su, J., Saravanapandian, V., Haditsch, U., Palmer, T.D., 2019. Females are not just 'Protected' Males": Sex-Specific vulnerabilities in placenta and brain after prenatal immune disruption (ENEURO). eNeuro 6, .0358-19.2019. https://doi.org/10.1523/ENEURO.0358-19.2019.

Bronson, S.L., Bale, T.L., 2014. Prenatal stress-induced increases in placental inflammation and offspring hyperactivity are Male-specific and ameliorated by maternal antiinflammatory treatment. Endocrinology 155, 2635–2646. https://doi.org/10.1210/EN.2014-1040.

Cameron, D., Mi, D., Vinh, N.N., Webber, C., Li, M., Marín, O., O'Donovan, M.C., Bray, N. J., 2023. Single-Nuclei RNA sequencing of 5 regions of the human prenatal brain implicates developing neuron populations in genetic risk for schizophrenia. Biol. Psychiatry 93, 157–166. https://doi.org/10.1016/J.BIOPSYCH.2022.06.033/ATTACHMENT/834F3B03-6D0E-4102-BC62-FBA9F8E0630D/MMC3.XLSX.

Canitano, R., Pallagrosi, M., 2017. Autism spectrum disorders and schizophrenia spectrum disorders: excitation/Inhibition imbalance and developmental trajectories. Front. Psychiatry 8, 69. https://doi.org/10.3389/FPSYT.2017.00069.

Chance, S.A., Casanova, M.F., Switala, A.E., Crow, T.J., 2008. Auditory cortex asymmetry, altered minicolumn spacing and absence of ageing effects in schizophrenia. Brain 131, 3178–3192. https://doi.org/10.1093/BRAIN/AWN211.

Choi, G.B., Yim, Y.S., Wong, H., Kim, Sangdoo, Kim, H., Kim, Sangwon V., Hoeffer, C.A., Littman, D.R., Huh, J.R., 2016. The maternal interleukin-17a pathway in mice promotes autism-like phenotypes in offspring. Science 351 (1979), 933–939. https://doi.org/10.1126/SCIENCE.AAD0314.

Clarkson-Townsend, D.A., Bales, K.L., Her, K.E., 2021. Developmental chronodisruption alters placental signaling in mice. PLOS ONE 16 (8), e0255296.

Costa-Mattioli, M., Monteggia, L.M., 2013. mTOR complexes in neurodevelopmental and neuropsychiatric disorders. Nat. Neurosci. 16, 1537–1543. https://doi.org/10.1038/NN.3546.

Courchesne, E., Mouton, P.R., Calhoun, M.E., Semendeferi, K., Ahrens-Barbeau, C., Hallet, M.J., Barnes, C.C., Pierce, K., 2011. Neuron number and size in prefrontal cortex of children with autism. JAMA 306, 2001–2010. https://doi.org/10.1001/JAMA.2011.1638.

Cowell, W., Deyssenroth, M., Chen, J., Wright, R.J., 2020. Maternal stress in relation to sex-specific expression of placental genes involved in nutrient transport, oxygen tension, immune response, and the glucocorticoid barrier. Placenta 96, 19–26. https://doi.org/10.1016/j.placenta.2020.05.004.

Curley, A.A., Arion, D., Volk, D.W., Asafu-Adjei, J.K., Sampson, A.R., Fish, K.N., Lewis, D. A., 2011. Cortical deficits of glutamic acid decarboxylase 67 expression in schizophrenia: clinical, protein, and cell type-specific features. Am. J. Psychiatry 168, 921–929. https://doi.org/10.1176/APPI.AJP.2011.11010052.

Deverman, B.E., Patterson, P.H., 2009. Cytokines and CNS development. Neuron 64, 61–78. https://doi.org/10.1016/j.neuron.2009.09.002.

Edgar, R.S., Stangherlin, A., Nagy, A.D., Nicoll, M.P., Efstathiou, S., O'Neill, J.S., Reddy, A.B., 2016. Cell autonomous regulation of herpes and influenza virus infection by the circadian clock. Proc. Natl. Acad. Sci. USA 113, 10085–10090. https://doi.org/10.1073/PNAS.1601895113/SUPPL_FILE/PNAS.1601895113.SM03.MOV.

Eltokhi, A., Janmaat, I.E., Genedi, M., Haarman, B.C.M., Sommer, I.E.C., 2020. Dysregulation of synaptic pruning as a possible link between intestinal microbiota dysbiosis and neuropsychiatric disorders. J. Neurosci. Res. 98, 1335–1369. https://doi.org/10.1002/JNR.24616.

Estes, M.L., McAllister, A.K., 2016. Maternal immune activation: implications for neuropsychiatric disorders. Science 353 (1979), 772–777. https://doi.org/10.1126/SCIENCE.AAG3194.

Fei, H., Lu, X., Shi, Z., Liu, X., Yang, C., Zhu, X., Lin, Y., Jiang, Z., Wang, J., Huang, D., Liu, L., Zhang, S., Jiang, L., 2025. Deciphering the preeclampsia-specific immune microenvironment and the role of pro-inflammatory macrophages at the maternal–fetal interface. Elife 13, RP100002. https://doi.org/10.7554/ELIFE.100002.

Fischer, M., Pereira, P.M., Holtmann, B., Simon, C.M., Hanauer, A., Heisenberg, M., Sendtner, M., 2009. P90 ribosomal s6 kinase 2 negatively regulates axon growth in motoneurons. Mol. Cell. Neurosci. 42, 134–141. https://doi.org/10.1016/j.mcn.2009.06.006.

Fitzgerald, E., Hor, K., Drake, A.J., 2020. Maternal influences on fetal brain development: the role of nutrition, infection and stress, and the potential for intergenerational consequences. Early Hum. Dev. 150, 105190. https://doi.org/10.1016/J.EARLHUMDEV.2020.105190.

Francés, L., Quintero, J., Fernández, A., Ruiz, A., Caules, J., Fillon, G., Hervás, A., Soler, C.V., 2022. Current state of knowledge on the prevalence of neurodevelopmental disorders in childhood according to the DSM-5: a systematic review in accordance with the PRISMA criteria. Child Adolesc. Psychiatry Ment. Health 16. https://doi.org/10.1186/S13034-022-00462-1.

Freedman, A.N., Clark, J., Eaves, L.A., Roell, K., Oran, A., Koval, L., Rager, J., Santos, H. P., Kuban, K., Joseph, R.M., Frazier, J., Marsit, C.J., Burt, A.A., O'Shea, T.M., Fry, R. C., 2023. A multi-omic approach identifies an autism spectrum disorder (ASD) regulatory complex of functional epimutations in placentas from children born preterm. Autism Res. 16, 918–934. https://doi.org/10.1002/AUR.2915.

Gadow, K.D., 2013. Association of schizophrenia spectrum and autism spectrum disorder (ASD) symptoms in children with ASD and clinic controls. Res. Dev. Disabil. 34, 1289–1299. https://doi.org/10.1016/J.RIDD.2013.01.011.

Ge, W., Wang, T., Zhao, Y., Yang, Y., Sun, Q., Yang, X., Gao, Y., Xu, X., Zhang, J., 2021. Period1 mediates rhythmic metabolism of toxins by interacting with CYP2E1, 12 Cell Death Dis. 12 (1), 1–13. https://doi.org/10.1038/s41419-020-03343-7.

Ghosh, S., Thamotharan, S., Fong, J., Lei, M.Y.Y., Janzen, C., Devaskar, S.U., 2024. Circulating extracellular vesicular microRNA signatures in early gestation show an association with subsequent clinical features of pre-eclampsia. Sci. Rep. 14, 16770. https://doi.org/10.1038/S41598-024-64057-W.

Glantz, L.A., Lewis, D.A., 2000. Decreased dendritic spine density on prefrontal cortical pyramidal neurons in schizophrenia. Arch. Gen. Psychiatry 57, 65–73. https://doi.org/10.1001/ARCHPSYC.57.1.65.

Gordon, R.J., McGregor, A.L., Connor, B., 2009. Chemokines direct neural progenitor cell migration following striatal cell loss. Mol. Cell. Neurosci. 41, 219–232. https://doi.org/10.1016/J.MCN.2009.03.001.

Gubbi, S., Quipildor, G.F., Barzilai, N., Huffman, D.M., Milman, S., 2018. 40 YEARS of IGF1: IGF1: the jekyll and hyde of the aging brain. J. Mol. Endocrinol. 61, T171–T185. https://doi.org/10.1530/JME-18-0093.

Hanna, J., Goldman-Wohl, D., Hamani, Y., Avraham, I., Greenfield, C., Natanson-Yaron, S., Prus, D., Cohen-Daniel, L., Arnon, T.I., Manaster, I., Gazit, R., Yutkin, V., Benharroch, D., Porgador, A., Keshet, E., Yagel, S., Mandelboim, O., 2006. Decidual NK cells regulate key developmental processes at the human fetal-maternal interface. Nat. Med. 12, 1065–1074. https://doi.org/10.1038/NM1452.

Hildebrand, D., Uhle, F., Sahin, D., Krauser, U., Weigand, M.A., Heeg, K., 2018. The interplay of notch signaling and STAT3 in TLR-activated human primary monocytes. Front. Cell Infect. Microbiol. 8, 382917. https://doi.org/10.3389/FCIMB.2018.00241/BIBTEX.

Hoyniak, C.P., Whalen, D.J., Luby, J.L., Barch, D.M., Miller, J.P., Zhao, P., Triplett, R.L., Ju, Y., El, Smyser, C.D., Warner, B., Rogers, C.E., Herzog, E.D., England, S.K., 2024. Sleep and circadian rhythms during pregnancy, social disadvantage, and alterations in brain development in neonates. Dev. Sci. 27. https://doi.org/10.1111/DESC.13456.

Hsiao, E.Y., Patterson, P.H., 2011. Activation of the maternal immune system induces endocrine changes in the placenta via IL-6. Brain Behav. Immun. 25, 604–615. https://doi.org/10.1016/j.bbi.2010.12.017.

Izuta, Y., Imada, T., Hisamura, R., Oonishi, E., Nakamura, S., Inagaki, E., Ito, M., Soga, T., Tsubota, K., 2017. Ketone body 3-hydroxybutyrate mimics calorie restriction via the Nrf2 activator, fumarate, in the retina. Aging Cell 17, e12699. https://doi.org/10.1111/ACEL.12699.

Jansson, T., Aye, I.L.M.H., Goberdhan, D.C.I., 2012. The emerging role of mTORC1 signalling in placental nutrient-sensing. Placenta 33, e23. https://doi.org/10.1016/J.PLACENTA.2012.05.010.

Joseph, T.T., Schuch, V., Hossack, D.J., Chakraborty, R., Johnson, E.L., 2024. Melatonin: the placental antioxidant and anti-inflammatory. Front. Immunol. 15, 1339304. https://doi.org/10.3389/FIMMU.2024.1339304.

Keepers, G.A., Fochtmann, L.J., Anzia, J.M., Benjamin, S., Lyness, J.M., Mojtabai, R., Servis, M., Walaszek, A., Buckley, P., Lenzenweger, M.F., Young, A.S., Degenhardt, A., Hong, S.H., 2020. The American psychiatric association practice guideline for the treatment of patients with schizophrenia. Am. J. Psychiatry 177, 868–872. https://doi.org/10.1176/APPI.AJP.2020.177901.

Kember, A.J., Elangainesan, P., Ferraro, Z.M., Jones, C., Hobson, S.R., 2023. Common sleep disorders in pregnancy: a review. Front. Med. (Lausanne) 10, 1235252. https://doi.org/10.3389/FMED.2023.1235252.

Kong, X., Gong, Z., Zhang, L., Sun, X., Ou, Z., Xu, B., Huang, J., Long, D., He, X., Lin, X., Li, Q., Xu, L., Xuan, A., 2019. JAK2/STAT3 signaling mediates IL-6-inhibited neurogenesis of neural stem cells through DNA demethylation/methylation. Brain Behav. Immun. 79, 159–173. https://doi.org/10.1016/j.bbi.2019.01.027.

Kostović, I., Radoš, M., Kostović-Srzentić, M., Krsnik, Ž., 2021. Fundamentals of the development of connectivity in the human fetal brain in late gestation: from 24 weeks gestational age to term. J. Neuropathol. Exp. Neurol. 80, 393–414. https://doi.org/10.1093/JNEN/NLAB024.

Kratimenos, P., Penn, A.A., 2019. Placental programming of neuropsychiatric disease. Pedia Res. 86, 157–164. https://doi.org/10.1038/S41390-019-0405-9.

Le Belle, J.E., Orozco, N.M., Paucar, A.A., Saxe, J.P., Mottahedeh, J., Pyle, A.D., Wu, H., Kornblum, H.I., 2011. Proliferative neural stem cells have high endogenous ROS levels that regulate self-renewal and neurogenesis in a PI3K/Akt-dependant manner. Cell Stem Cell 8, 59–71. https://doi.org/10.1016/j.stem.2010.11.028.

Lewis, S.A., Bakhtiari, S., Forstrom, J., Bayat, A., Bilan, F., Le Guyader, G. l, Alkhunaizi, E., Vernon, H., Padilla-Lopez, S.R., Kruer, M.C., 2023. AGAP1-associated endolysosomal trafficking abnormalities link gene–environment interactions in neurodevelopmental disorders (dmm). Dis. Model Mech. 16, 049838. https://doi.org/10.1242/DMM.049838.

Liu, A., Huoshen, W., Wang, Y., Yi, S., Qin, Z., 2025. Exploration of circadian Clock-Related genes in the pathogenesis of psoriatic arthritis to identify potential therapeutic targets from Multi-Omics insight: a mendelian randomization study. Int. J. Rheum. Dis. 28, e70158. https://doi.org/10.1111/1756-185X.70158.

Long, J.E., Drayson, M.T., Taylor, A.E., Toellner, K.M., Lord, J.M., Phillips, A.C., 2016. Morning vaccination enhances antibody response over afternoon vaccination: a cluster-randomised trial. Vaccine 34, 2679–2685. https://doi.org/10.1016/j.vaccine.2016.04.032.

Loomes, R., Hull, L., Mandy, W.P.L., 2017. What is the male-to-female ratio in autism spectrum disorder? A systematic review and meta-analysis. J. Am. Acad. Child Adolesc. Psychiatry 56, 466–474. https://doi.org/10.1016/j.jaac.2017.03.013.

Louvi, A., Artavanis-Tsakonas, S., 2006. Notch signalling in vertebrate neural development. Nat. Rev. Neurosci. 7 (2), 93–102. https://doi.org/10.1038/nrn1847.

Love, C., Sominsky, L., O'Hely, M., Berk, M., Vuillermin, P., Dawson, S.L., 2024. Prenatal environmental risk factors for autism spectrum disorder and their potential mechanisms. BMC Med. 22, 393. https://doi.org/10.1186/S12916-024-03617-3.

Luo, Z., Tian, M., Yang, G., Tan, Q., Chen, Y., Li, G., Zhang, Q., Li, Y., Wan, P., Wu, J., 2022. Hypoxia signaling in human health and diseases: implications and prospects for therapeutics. Signal Transduct. Target. Ther. 7 (1), 1–30. https://doi.org/10.1038/s41392-022-01080-1.

Machado-Neto, J.A., Fenerich, B.A., Rodrigues Alves, A.P.N., Fernandes, J.C., Scopim-Ribeiro, R., Coelho-Silva, J.L., Traina, F., 2018. Insulin substrate receptor (IRS) proteins in normal and malignant hematopoiesis. Clinics 73. https://doi.org/10.6061/CLINICS/2018/E566S.

Mansell, T., Ponsonby, A.L., Januar, V., Novakovic, B., Collier, F., Burgner, D., Vuillermin, P., Ryan, J., Saffery, R., Carlin, J., Allen, K., Tang, M., Ranganathan, S.,

Dwyer, T., Jachno, K., Sly, P., 2019. Early-life determinants of hypoxia-inducible factor 3A gene (HIF3A) methylation: a birth cohort study. Clin. Epigenetics 11, 96. https://doi.org/10.1186/S13148-019-0687-0.

Méndez, I., Vázquez-Martínez, O., Hernández-Muñoz, R., Valente-Godínez, H., Díaz-Muñoz, M., 2016. Redox regulation and pro-oxidant reactions in the physiology of circadian systems. Biochimie 124, 178–186. https://doi.org/10.1016/J.BIOCHI.2015.04.014.

Miyata, J., Hirao, K., Namiki, C., Fujiwara, H., Shimizu, M., Fukuyama, H., Sawamoto, N., Hayashi, T., Murai, T., 2009. Reduced White matter integrity correlated with cortico–subcortical gray matter deficits in schizophrenia. Schizophr. Res. 111, 78–85. https://doi.org/10.1016/J.SCHRES.2009.03.010.

Mouat, J.S., Li, X., Neier, K., Zhu, Y., Mordaunt, C.E., La Merrill, M.A., Lehmler, H.J., Jones, M.P., Lein, P.J., Schmidt, R.J., LaSalle, J.M., 2023. Networks of placental DNA methylation correlate with maternal serum PCB concentrations and child neurodevelopment. Environ. Res. 220. https://doi.org/10.1016/j.envres.2023.115227.

Myatt, L., Cui, X., 2004. Oxidative stress in the placenta. Histochem. Cell Biol. 122, 369–382. https://doi.org/10.1007/S00418-004-0677-X.

Myung, J., Vitet, H., Truong, V.H., Ananthasubramaniam, B., 2025. The role of the multiplicity of circadian clocks in mammalian systems. Sleep. Med. 131, 106518. https://doi.org/10.1016/J.SLEEP.2025.106518.

Nagai, N., Ayaki, M., Yanagawa, T., Hattori, A., Negishi, K., Mori, T., Nakamura, T.J., Tsubota, K., 2019. Suppression of blue light at night ameliorates metabolic abnormalities by controlling circadian rhythms. Invest Ophthalmol. Vis. Sci. 60, 3786–3793. https://doi.org/10.1167/IOVS.19-27195.

Nguyen, K.D., et al., 2013. Circadian Gene *Bmal1* Regulates Diurnal Oscillations of Ly6C^{hi} Inflammatory Monocytes. Science 341, 1483–1488. https://doi.org/10.1126/science.1240636.

Nowakowski, T.J., Bhaduri, A., Pollen, A.A., Alvarado, B., Mostajo-Radji, M.A., Di Lullo, E., Haeussler, M., Sandoval-Espinosa, C., Liu, S.J., Velmeshev, D., Ounadjela, J.R., Shuga, J., Wang, X., Lim, D.A., West, J.A., Leyrat, A.A., Kent, W.J., Kriegstein, A.R., 2017. Spatiotemporal gene expression trajectories reveal developmental hierarchies of the human cortex. Science (1979) 358 13181323. https://doi.org/10.1126/SCIENCE.AAP8809/SUPPL_FILE/AAP8809_NOWAKOWSKI_SM-TABLES-S1-S11.XLSX.

Nugent, B.M., O'Donnell, C.M., Epperson, C.N., Bale, T.L., 2018. Placental H3K27me3 establishes female resilience to prenatal insults. Nat. Commun. 2018 9 (1), 1–10. https://doi.org/10.1038/s41467-018-04992-1.

Núñez Estevez, K.J., Rondón-Ortiz, A.N., Nguyen, J.Q.T., Kentner, A.C., 2020. Environmental influences on placental programming and offspring outcomes following maternal immune activation. Brain Behav. Immun. 83, 44–55. https://doi.org/10.1016/J.BBI.2019.08.192.

O'Donnell, K.J., Meaney, M.J., 2017. Fetal origins of mental health: the developmental origins of health and disease hypothesis. Am. J. Psychiatry 174, 319–328. https://doi.org/10.1176/APPI.AJP.2016.16020138.

Oishi, A., Karamitri, A., Gerbier, R., Lahuna, O., Ahmad, R., Jockers, R., 2017. Orphan GPR61, GPR62 and GPR135 receptors and the melatonin MT2 receptor reciprocally modulate their signaling functions. Sci. Rep. 7, 1–15. https://doi.org/10.1038/S41598-017-08996-7;TECHMETA=109.

Osman, H.C., Moreno, R., Rose, D., Rowland, M.E., Ciernia, A.V., Ashwood, P., 2024. Impact of maternal immune activation and sex on placental and fetal brain cytokine and gene expression profiles in a preclinical model of neurodevelopmental disorders. J. Neuroinflamm. 21, 1–14. https://doi.org/10.1186/S12974-024-03106-7/FIGURES/5.

Ouzzani, M., Hammady, H., Fedorowicz, Z., Elmagarmid, A., 2016. Rayyan-a web and mobile app for systematic reviews. Syst. Rev. 5, 1–10. https://doi.org/10.1186/S13643-016-0384-4/FIGURES/6.

Page, M.J., McKenzie, J.E., Bossuyt, P.M., Boutron, I., Hoffmann, T.C., Mulrow, C.D., Shamseer, L., Tetzlaff, J.M., Akl, E.A., Brennan, S.E., Chou, R., Glanville, J., Grimshaw, J.M., Hróbjartsson, A., Lalu, M.M., Li, T., Loder, E.W., Mayo-Wilson, E., McDonald, S., McGuinness, L.A., Stewart, L.A., Thomas, J., Tricco, A.C., Welch, V.A., Whiting, P., Moher, D., 2021. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. PLoS Med 18, e1003583. https://doi.org/10.1371/JOURNAL.PMED.1003583.

Pang, W., Yi, X., Li, L., Liu, L., Xiang, W., Xiao, L., 2021. Untangle the multi-facet functions of Auts2 as an entry point to understand neurodevelopmental disorders. Front. Psychiatry 12, 580433.

Parenti, M., Schmidt, R.J., Ozonoff, S., Shin, H.M., Tancredi, D.J., Krakowiak, P., Hertz-Picciotto, I., Walker, C.K., Slupsky, C.M., 2022. Maternal serum and placental metabolomes in association with prenatal phthalate exposure and neurodevelopmental outcomes in the MARBLES cohort. Metabolites 12. https://doi.org/10.3390/METABO12090829.

Parenti, M., Schmidt, R.J., Tancredi, D.J., Hertz-Picciotto, I., Walker, C.K., Slupsky, C.M., 2024. Neurodevelopment and metabolism in the Maternal-Placental-Fetal unit. e2413399 JAMA Netw. Open 7, e2413399. https://doi.org/10.1001/JAMANETWORKOPEN.2024.13399.

Pavlov, O.V., Selutin, A.V., Pavlova, O.M., Selkov, S.A., 2020. Two patterns of cytokine production by placental macrophages. Placenta 91, 1–10. https://doi.org/10.1016/J.PLACENTA.2020.01.005.

Pereira, R.D., De Long, N.E., Wang, R.C., Yazdi, F.T., Holloway, A.C., Raha, S., 2015. Angiogenesis in the placenta: the role of reactive oxygen species signaling. Biomed. Res Int 2015. https://doi.org/10.1155/2015/814543.

Pringle, K.G., Kind, K.L., Sferruzzi-Perri, A.N., Thompson, J.G., Roberts, C.T., 2010. Beyond oxygen: complex regulation and activity of hypoxia inducible factors in pregnancy. Hum. Reprod. Update 16, 415–431. https://doi.org/10.1093/HUMUPD/DMP046.

Rahimi, M.J., Urban, N., Wegler, M., Sticht, H., Schaefer, M., Popp, B., Gaunitz, F., Morleo, M., Nigro, V., Maitz, S., Mancini, G.M.S., Ruivenkamp, C., Suk, E.K., Bartolomaeus, T., Merkenschlager, A., Koboldt, D., Bartholomew, D., Stegmann, A.P. A., Sinnema, M., Duynisveld, I., Salvarinova, R., Race, S., de Vries, B.B.A., Trimouille, A., Naudion, S., Marom, D., Hamiel, U., Henig, N., Demurger, F., Rahner, N., Bartels, E., Hamm, J.A., Putnam, A.M., Person, R., Abou Jamra, R., Oppermann, H., 2022. De novo variants in ATP2B1 lead to neurodevelopmental delay. Am. J. Hum. Genet. 109, 944–952. https://doi.org/10.1016/J.AJHG.2022.03.009.

Rosenfeld, C.S., 2020. The Placenta-Brain-Axis. J. Neurosci. Res. 99, 271. https://doi.org/10.1002/JNR.24603.

Santos, H.P., Bhattacharya, A., Joseph, R.M., Smeester, L., Kuban, K.C.K., Marsit, C.J., O'Shea, T.M., Fry, R.C., 2020. Evidence for the placenta-brain axis: multi-omic kernel aggregation predicts intellectual and social impairment in children born extremely preterm. Mol. Autism 11, 97. https://doi.org/10.1186/S13229-020-00402-W.

Scheiermann, C., Kunisaki, Y., Frenette, P.S., 2013. Circadian control of the immune system. Nat. Rev. Immunol. 13 (3), 190–198. https://doi.org/10.1038/nri3386.

Schmidt, R.J., Schroeder, D.I., Crary-Dooley, F.K., Barkoski, J.M., Tancredi, D.J., Walker, C.K., Ozonoff, S., Hertz-Picciotto, I., Lasalle, J.M., 2016. Self-reported pregnancy exposures and placental DNA methylation in the MARBLES prospective autism sibling study. Environ. Epigenet. 2. https://doi.org/10.1093/EEP/DVW024.

Schroeder, D.I., Schmidt, R.J., Crary-Dooley, F.K., Walker, C.K., Ozonoff, S., Tancredi, D. J., Hertz-Picciotto, I., LaSalle, J.M., 2016. Placental methylome analysis from a prospective autism study. Mol. Autism 7. https://doi.org/10.1186/S13229-016-0114-8.

Sebastiani, G., Navarro-Tapia, E., Almeida-Toledano, L., Serra-Delgado, M., Paltrinieri, A.L., García-Algar, Ó., Andreu-Fernández, V., 2022. Effects of antioxidant intake on fetal development and Maternal/Neonatal health during pregnancy. Antioxidants 11, 648. https://doi.org/10.3390/ANTIOX11040648/S1.

Selemon, L.D., Zecevic, N., 2015. Schizophrenia: a tale of two critical periods for prefrontal cortical development. Transl. Psychiatry 5 (8), e623. https://doi.org/10.1038/tp.2015.115.

Sferruzzi-Perri, A.N., Camm, E.J., 2016. The programming power of the placenta. Front. Physiol. 7. https://doi.org/10.3389/FPHYS.2016.00033.

Soullane, S., Spence, A.R., Abenhaim, H.A., 2022. Association of placental pathology and gross morphology with autism spectrum disorders. Autism Res. 15, 531–538. https://doi.org/10.1002/AUR.2658.

Stallone, G., Matteo, M., Netti, G.S., Infante, B., Di Lorenzo, A., Prattichizzo, C., Carlucci, S., Trezza, F., Gesualdo, L., Greco, P., Grandaliano, G., 2017. Semaphorin 3F expression is reduced in pregnancy complicated by preeclampsia. An observational clinical study. PLoS One 12, e0174400. https://doi.org/10.1371/JOURNAL.PONE.0174400.

Stoner, R., Chow, M.L., Boyle, M.P., Sunkin, S.M., Mouton, P.R., Roy, S., Wynshaw-Boris, A., Colamarino, S.A., Lein, E.S., Courchesne, E., 2014. Patches of disorganization in the neocortex of children with autism. N. Engl. J. Med. 370, 1209–1219. https://doi.org/10.1056/NEJMOA1307491.

Straughen, J.K., Misra, D.P., Divine, G., Shah, R., Perez, G., VanHorn, S., Onbreyt, V., Dygulska, B., Schmitt, R., Lederman, S., Narula, P., Salafia, C.M., 2017. The association between placental histopathology and autism spectrum disorder. Placenta 57, 183–188. https://doi.org/10.1016/j.placenta.2017.07.006.

Strohmaier, S., Devore, E.E., Vetter, C., Eliassen, A.H., Rosner, B., Okereke, O.I., Schernhammer, E.S., 2019. Night shift work before and during pregnancy in relation to depression and anxiety in adolescent and young adult offspring. Eur. J. Epidemiol. 34, 625. https://doi.org/10.1007/S10654-019-00525-2.

Study Quality Assessment Tools | NHLBI, NIH [WWW Document], n.d. URL https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools (accessed 8.31.25).

Stumm, R.K., Zhou, C., Ara, T., Lazarini, F., Dubois-Dalcq, M., Nagasawa, T., Höllt, V., Schulz, S., 2003. CXCR4 regulates interneuron migration in the developing neocortex. J. Neurosci. 23, 5123–5130. https://doi.org/10.1523/JNEUROSCI.23-12-05123.2003.

Sun, P., Wang, M., Chai, X., Liu, Y.X., Li, L., Zheng, W., Chen, S., Zhu, X., Zhao, S., 2025. Disruption of tryptophan metabolism by high-fat diet-triggered maternal immune activation promotes social behavioral deficits in Male mice. Nat. Commun. 16, 2105. https://doi.org/10.1038/S41467-025-57414-4.

Suzuki, I.K., Gacquer, D., Van Heurck, R., Kumar, D., Wojno, M., Bilheu, A., Herpoel, A., Lambert, N., Cheron, J., Polleux, F., Detours, V., Vanderhaeghen, P., 2018. Human-Specific NOTCH2NL genes expand cortical neurogenesis through Delta/Notch regulation. Cell 173, 1370. https://doi.org/10.1016/J.CELL.2018.03.067.

Takata, T., Araki, S., Tsuchiya, Y., Watanabe, Y., 2020. Oxidative stress orchestrates MAPK and Nitric-Oxide synthase signal. Int. J. Mol. Sci. 8750 (21), 8750. https://doi.org/10.3390/IJMS21228750.

Tang, G., Gudsnuk, K., Kuo, S.H., Cotrina, M.L., Rosoklija, G., Sosunov, A., Sonders, M.S., Kanter, E., Castagna, C., Yamamoto, A., Yue, Z., Arancio, O., Peterson, B.S., Champagne, F., Dwork, A.J., Goldman, J., Sulzer, D., 2014. Loss of mTOR-Dependent macroautophagy causes Autistic-like synaptic pruning deficits. Neuron 83, 1131–1143. https://doi.org/10.1016/j.neuron.2014.07.040.

Tiveron, M.C., Rossel, M., Moepps, B., Yong, L.Z., Seidenfaden, R., Favor, J., König, N., Cremer, H., 2006. Molecular interaction between projection neuron precursors and invading interneurons via Stromal-Derived factor 1 (CXCL12)/CXCR4 signaling in the cortical subventricular Zone/Intermediate zone. J. Neurosci. 26, 13273. https://doi.org/10.1523/JNEUROSCI.4162-06.2006.

Ursini, G., Di Carlo, P., Mukherjee, S., Chen, Q., Han, S., Kim, J., Deyssenroth, M., Marsit, C.J., Chen, J., Hao, K., Punzi, G., Weinberger, D.R., 2023. Prioritization of

potential causative genes for schizophrenia in placenta. Nat. Commun. 14 (1), 1–17. https://doi.org/10.1038/s41467-023-38140-1.

Ursini, G., Punzi, G., Chen, Q., Marenco, S., Robinson, J.F., Porcelli, A., Hamilton, E.G., Mitjans, M., Maddalena, G., Begemann, M., Seidel, J., Yanamori, H., Jaffe, A.E., Berman, K.F., Egan, M.F., Straub, R.E., Colantuoni, C., Blasi, G., Hashimoto, R., Rujescu, D., Ehrenreich, H., Bertolino, A., Weinberger, D.R., 2018. Convergence of placenta biology and genetic risk for schizophrenia article. Nat. Med. 24, 792–801. https://doi.org/10.1038/S41591-018-0021-Y;KWRD=BIOMEDICINE.

Ursini, G., Punzi, G., Langworthy, B.W., Chen, Q., Xia, K., Cornea, E.A., Goldman, B.D., Styner, M.A., Knickmeyer, R.C., Gilmore, J.H., Weinberger, D.R., 2021. Placental genomic risk scores and early neurodevelopmental outcomes. Proc. Natl. Acad. Sci. USA 118. https://doi.org/10.1073/PNAS.2019789118/-/DCSUPPLEMENTAL.

Vacher, C.M., Lacaille, H., O'Reilly, J.J., Salzbank, J., Bakalar, D., Sebaoui, S., Liere, P., Clarkson-Paredes, C., Sasaki, T., Sathyanesan, A., Kratimenos, P., Ellegood, J., Lerch, J.P., Imamura, Y., Popratiloff, A., Hashimoto-Torii, K., Gallo, V., Schumacher, M., Penn, A.A., 2021. Placental endocrine function shapes cerebellar development and social behavior. Nat. Neurosci. 24, 1392–1401. https://doi.org/10.1038/S41593-021-00896-4;SUBJMETA=1689,2571,378,631;KWRD=DEVELOPMENT+OF+THE+NERVOUS+SYSTEM,DISEASES+OF+THE+NERVOUS+SYSTEM.

van Otterdijk, S.D., Binder, A.M., Michels, K.B., 2024. Placental methylation and pro-inflammatory protein levels in cord blood. Placenta 158, 231–239. https://doi.org/10.1016/J.PLACENTA.2024.10.067.

Voiculescu, S.E., Zygouropoulos, N., Zahiu, C.D., Zagrean, A.M., 2014. Role of melatonin in embryo fetal development. J. Med. Life 7, 488.

Waddell, B.J., Wharfe, M.D., Crew, R.C., Mark, P.J., 2012. A rhythmic placenta? Circadian variation, clock genes and placental function. Placenta 33, 533–539. https://doi.org/10.1016/j.placenta.2012.03.008.

Willsey, A.J., Sanders, S.J., Li, M., Dong, S., Tebbenkamp, A.T., Muhle, R.A., Reilly, S.K., Lin, L., Fertuzinhos, S., Miller, J.A., Murtha, M.T., Bichsel, C., Niu, W., Cotney, J., Ercan-Sencicek, A.G., Gockley, J., Gupta, A.R., Han, W., He, X., Hoffman, E.J., Klei, L., Lei, J., Liu, W., Liu, L., Lu, C., Xu, X., Zhu, Y., Mane, S.M., Lein, E.S., Wei, L., Noonan, J.P., Roeder, K., Devlin, B., Sestan, N., State, M.W., 2013. Coexpression networks implicate human midfetal deep cortical projection neurons in the pathogenesis of autism. Cell 155, 997–1007. https://doi.org/10.1016/J.CELL.2013.10.020.

Wilson, C., González-Billault, C., 2015. Regulation of cytoskeletal dynamics by redox signaling and oxidative stress: implications for neuronal development and trafficking. Front. Cell Neurosci. 9. https://doi.org/10.3389/FNCEL.2015.00381.

Wu, Y., Zhang, H., Wang, C., Broekman, B.F.P., Chong, Y.S., Shek, L.P., Gluckman, P.D., Meaney, M.J., Fortier, M.V., Qiu, A., 2020. Inflammatory modulation of the associations between prenatal maternal depression and neonatal brain. Neuropsychopharmacology 46 (2), 470–477. https://doi.org/10.1038/s41386-020-0774-0.

Xie, Y., Ba, L., Wang, M., Deng, S.Y., Chen, S.M., Huang, L.F., Zhang, M., Wang, W., Ding, F.F., 2019. Chronic sleep fragmentation shares similar pathogenesis with neurodegenerative diseases: Endosome-autophagosome-lysosome pathway dysfunction and microglia-mediated neuroinflammation. CNS Neurosci. Ther. 26, 215. https://doi.org/10.1111/CNS.13218.

Yap, P., Riley, L.G., Kakadia, P.M., Bohlander, S.K., Curran, B., Rahimi, M.J., Alburaiky, S., Hayes, I., Oppermann, H., Print, C., Cooper, S.T., Le Quesne Stabej, P., 2023. Biallelic ATP2B1 variants as a likely cause of a novel neurodevelopmental malformation syndrome with primary hypoparathyroidism. Eur. J. Hum. Genet. 32 (1), 125–129. https://doi.org/10.1038/s41431-023-01484-9.

Youm, Y.H., Nguyen, K.Y., Grant, R.W., Goldberg, E.L., Bodogai, M., Kim, D., D'Agostino, D., Planavsky, N., Lupfer, C., Kanneganti, T.D., Kang, S., Horvath, T.L., Fahmy, T.M., Crawford, P.A., Biragyn, A., Alnemri, E., Dixit, V.D., 2015. Ketone body β-hydroxybutyrate blocks the NLRP3 inflammasome-mediated inflammatory disease. Nat. Med. 21, 263. https://doi.org/10.1038/NM.3804.

Yuen, N., Lemaire, M., Wilson, S.L., 2024. Cell-free placental DNA: what do we really know? PLoS Genet. 20, e1011484. https://doi.org/10.1371/JOURNAL.PGEN.1011484.

Zhang, Y., Lahmann, I., Baum, K., Shimojo, H., Mourikis, P., Wolf, J., Kageyama, R., Birchmeier, C., 2021. Oscillations of Delta-like1 regulate the balance between differentiation and maintenance of muscle stem cells. Nat. Commun. 12 (1), 1–16. https://doi.org/10.1038/s41467-021-21631-4.

Zhang, X., Wei, H., 2021. Role of decidual natural killer cells in human pregnancy and related pregnancy complications. Front. Immunol. 12, 728291. https://doi.org/10.3389/FIMMU.2021.728291.

Zhu, Y., Gomez, J.A., Laufer, B.I., Mordaunt, C.E., Mouat, J.S., Soto, D.C., Dennis, M.Y., Benke, K.S., Bakulski, K.M., Dou, J., Marathe, R., Jianu, J.M., Williams, L.A., Gutierrez Fugón, O.J., Walker, C.K., Ozonoff, S., Daniels, J., Grosvenor, L.P., Volk, H. E., Feinberg, J.I., Fallin, M.D., Hertz-Picciotto, I., Schmidt, R.J., Yasui, D.H., LaSalle, J.M., 2022. Placental methylome reveals a 22q13.33 brain regulatory gene locus associated with autism. Genome Biol. 23 (1), 1–32. https://doi.org/10.1186/S13059-022-02613-1.

Zhu, Y., Mordaunt, C.E., Yasui, D.H., Marathe, R., Coulson, R.L., Dunaway, K.W., Jianu, J.M., Walker, C.K., Ozonoff, S., Hertz-Picciotto, I., Schmidt, R.J., Lasalle, J.M., 2019. Placental DNA methylation levels at CYP2E1 and IRS2 are associated with child outcome in a prospective autism study. Hum. Mol. Genet. 28, 2659–2674. https://doi.org/10.1093/HMG/DDZ084.