Symposium

Placental–Neural Cross Talk: Biological Mechanisms Shaping Brain Architecture

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Impact of placental function on normal and pathological brain processes and supported behavior is an integrative research area dubbed "neuroplacentology." Placental functional genetics, structure, and vascular function have been discovered to have links to multiple clinical outcomes: autism, schizophrenia, and developmental cognitive impairment in offspring and postpartum depression and cognition in mothers. There are significant data showing that long-term impacts of preterm birth, diseases of pregnancy (preeclampsia), and maternal stress and depression may all be mediated by placental mechanisms, providing clinical and translational insights. Here, we will provide an up-to-date introduction to this emerging field. Mechanistic links between variations in placental structure and function and features of human and animal brain development and function will be discussed, clarifying basic biological connections and highlighting new targets to prevent clinical impairments.

Introduction

Neuroplacentology, our mini-symposium topic, focuses on understanding how the bidirectional placenta–brain axis shapes both immediate and long-term aspects of brain development and neurological function (Fig. 1; Kratimenos and Penn, 2019; Rosenfeld, 2021; Vacher et al., 2023). The placenta is a transient fetal-maternal interface that regulates the in utero environment by controlling gas exchange, nutrition, waste removal, endocrine and inflammatory signaling, and other exogenous exposures. Placental function is critical to fetal development, particularly to the developing brain. Reliance on the placenta as both an interface and active regulator of the in utero environment makes the rapidly developing fetal brain particularly vulnerable to placental dysfunction or placental responses to adverse environmental signals. Linking adverse perinatal events and later pathology, in this case mediated by signals from placenta to brain, is one aspect of the "fetal origins of disease" hypothesis (Barker et al., 1989). While this hypothesis originally proposed that adverse prenatal events can program physiological processes that manifest later in life as metabolic and cardiovascular dysfunction, it can now be extended to neuropsychiatric outcomes such as autism spectrum disorder (ASD), schizophrenia, depression, and neurodegeneration (Bale et al., 2010).

Brain development is a highly orchestrated process that relies on precise timing of cell generation, migration, and circuit establishment (Tau and Peterson, 2010). Developmental neuroscience has tended to focus on the self-assembly of the fetal brain, neglecting the critical role of the placenta as a neurodevelopmental organizer under both normal and pathological conditions. Neuroscientists need to know about the placenta because it directly controls multiple aspects of brain assembly and can program later neurodevelopmental disorders both directly and indirectly (Goeden et al., 2016; Vacher et al., 2021; Nichols et al., 2024; Carver et al., 2025; Gumusoglu et al., 2025; Mir et al., 2025; Troncoso et al., 2026). It is also an accessible tissue that may allow early prediction of future neurodevelopmental risks during pregnancy—via measurements of placental products in maternal circulation such as placentally derived hormones (Bilder et al., 2019; Kosidou et al., 2024; Bakhireva et al., 2025) or placental extracellular vesicles (Mitchell et al., 2015; Hodyl et al., 2017; Gall et al., 2022; Patel et al., 2025)—or at the time of birth (Raghavan et al., 2019; Penn et al., 2021; Chen and Shenoy, 2022; Spinillo et al., 2023).

The placenta forms from fetal cells that invade the maternal uterine wall, deeply in humans and shallowly in mice, to create a vascular circuit that approximates two separate vascular systems (Carter et al., 2007; Maltepe and Fisher, 2015). This structure prevents physical mixing of the maternal and fetal blood but provides the opportunity for signaling via direct transport or secretion of signaling molecule or via extracellular vesicles. The human term placenta receives up to 10% of maternal cardiac output to ensure that the fetus has continuous nutrient, gas, and waste exchange. The invasive nature of this placentation process requires extensive remodeling of the uterine blood vessels. Failure of this remodeling can lead to major pregnancy

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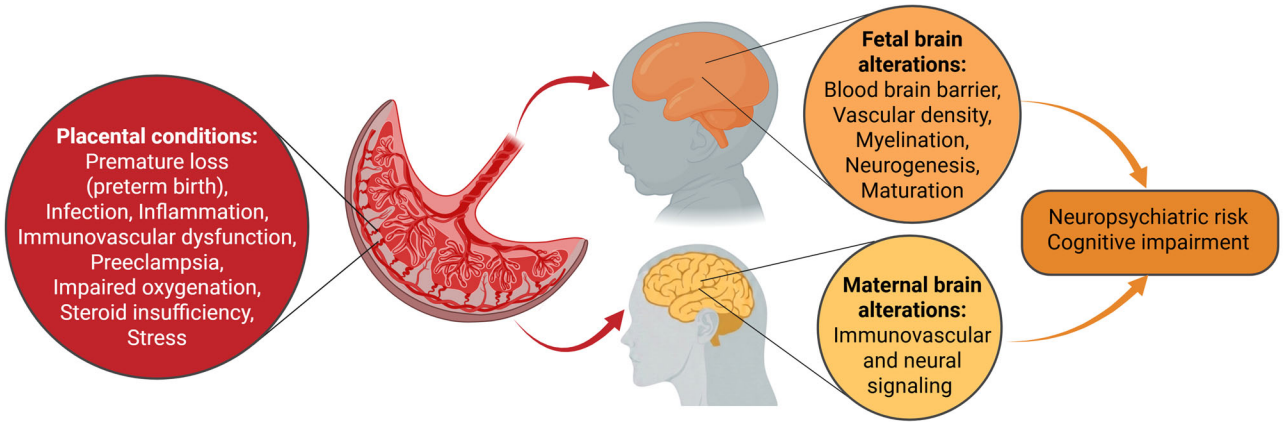


Figure 1. Mechanisms and impacts of placental disruption on the brain.

complications such as preeclampsia, a multisystem disorder characterized by maternal hypertension and renal damage that can result in maternal seizures or stroke and impaired fetal growth or the need for preterm delivery (Ives et al., 2020; Redman et al., 2022). Intrauterine growth restriction from preeclampsia and other causes is associated with a significantly increased risk of poor neurodevelopmental outcomes (Nomura et al., 2017; Gumusoglu et al., 2020). Placental vessels have no autonomic or other nerve innervation (Marzioni et al., 2004) so placental vascular tone is controlled by circulating vasoactive factors (including prostaglandins and endothelins) primarily made by the placenta (Esposito et al., 2025).

This placental secretory function extends well beyond vascular control; the placenta is the first mature endocrine organ of the fetus (Costa, 2016) and its first immune interface (Mor, 2022). It produces a vast array of neuroactive peptides (including early production of neurotransmitters), steroid hormones, chemokines, and cytokines. These factors must be expressed during critical windows to support neuronal and glial development and ultimately to ensure establishment of normal neural circuitry. Misexpression of these endogenous placental factors may be detrimental to placental physiology, as well as directly altering neurodevelopmental processes. Exogenous factors, such as maternal infection, inflammation, or stress, can also alter placental physiology and signaling. In addition, maternal undernutrition or metabolic dysregulation, including obesity and gestational diabetes, can directly impact fetal growth but also alter placental physiology (Shook et al., 2020; Satterfield et al., 2021) creating additional risks for the developing brain. Understanding the connection between placental physiology and specific aspects of neurodevelopment is key to understanding the origins of many neuropsychiatric outcomes.

Initial work on the placenta–brain axis focused primarily on correlations between placental histopathology and abnormal neurodevelopmental outcomes (Klebanoff, 2009; Redline, 2022). In recent decades, mechanistic understanding of the placenta–brain axis has begun to emerge through use of new animal models and human brain organoids that directly test the impact of specific placental factors on brain regions, circuits, and outcomes. Bringing human and preclinical models together allows for mechanistic investigation with assessment of translational relevance, but it is important to be aware of the limitations of cross-species comparisons (Aye et al., 2025; Vacher et al., 2025). Humans, primates, and rodents have hemochorial discoid placentas in which the fetal chorionic tissue is in direct contact with circulating maternal blood. However, their anatomical arrangement of cells differs, across species the developmental patterns of gene expression vary, and production of placental hormones, especially steroids, can differ significantly (Malassine et al., 2003; Cox et al., 2009; Hemberger et al., 2020). Developmental time points between human and mouse brain development during gestation also do not map precisely to one another, with the mouse brain being less mature than human in many regions at the time of birth and associated placental loss (Khodosevich and Sellgren, 2023). Despite these differences, multiple functional properties are conserved, including the integrated maternal-fetal-placental unit, functional properties of placental hormone-secreting cells (e.g., syncytiotrophoblasts), and specific windows of prenatal programming (Aguilera et al., 2022).

In our symposium and in this synopsis of the science it encapsulates, we explore multiple intersecting aspects of this emerging field of neuroplacentology, with a particular focus on several conditions in which this biology has significant consequences: preterm birth, inflammation, and preeclampsia. The studies presented here move from clinical associations to mechanistic insight by integrating evidence from neonatal cohorts, human imaging, and experimental models. Starting with clinical work from the Mir lab (Mir et al., 2025), imaging studies from extremely preterm infants show that a specifically fetal inflammatory response (FIR) in the placenta and umbilical cord, distinct from maternal inflammation, is independently associated with abnormal brain imaging—especially in white matter and cerebellum—separate from the impact of preterm birth, suggesting that fetal-placental inflammation alters human brain vulnerability via a "multi-hit" mechanism. Mechanistic studies from the Bonnin lab (Goeden et al., 2016; Zhao et al., 2022) demonstrate how early maternal immune activation (MIA) can alter fetal neurodevelopment through placental signals that modify both placental serotonin delivery and blood–brain barrier (BBB) maturation, with the striking finding that prostaglandin-mediated neurovascular dysfunction in this model has lasting vascular consequences. Work of Vacher, Penn, and colleagues (Vacher et al., 2021; Salzbank et al., 2025) identify the placenta-derived neuroactive steroid allopregnanolone as a critical endocrine regulator of developmental GABAergic tone, immune–glia states, and myelination trajectories, providing causal evidence that placental allopregnanolone insufficiency drives sex- and region-specific phenotypes including ASD-relevant behaviors. These mechanistic studies also highlight the narrow dose/timing windows that may be required for therapeutic rescue. Work from the

Escudero lab (Troncoso et al., 2023; Troncoso et al., 2026) extends these mechanisms to preeclampsia, identifying placental vascular dysfunction as a source of early neurovascular imprinting in offspring, with effects on angiogenesis, cerebral perfusion, BBB integrity, and later cognition. Nichols and colleagues (Nichols et al., 2024) show that even in otherwise uncomplicated pregnancies, placental oxygenation moderates the relationship between maternal stress and fetal cortical development, suggesting that placental physiology may influence brain morphogenesis below the threshold of overt disease. Finally, recent Gumusoglu lab findings (Gumusoglu et al., 2025) shift the axis to the maternal brain, suggesting that preeclampsia-associated placental immunovascular signals alter maternal hypothalamic, cortical, and hippocampal biology and may contribute to neuropsychiatric and cognitive risk not only in the fetus and child, but also during maternal life.

Neuroimaging Abnormalities Are Associated with Placental Pathological Evidence of Fetal Inflammatory Responses in Extremely Preterm Infants (Mir)

The placenta is an important window into maternal and fetal biology, particularly in pregnancies marked by perinatal adversity, linking perinatal biology to brain development. Extremely preterm birth occurs just after mid-gestation, a time when inflammatory exposures are a part of both injury and maturation of the developing brain (Hillier et al., 1991; Romero et al., 1998; Klein and Gibbs, 2005; Salas et al., 2013; Stinson and Payne, 2019; Jung et al., 2020). FIR syndrome is a biologically plausible bridge between intrauterine infection, systemic fetal immune activation including the placenta, and infant structural brain outcomes (Mir et al., 2025). While chorioamnionitis—inflammation of the amniotic sac and/or chorion (the membrane of placental origin)—has long been linked to preterm brain injury, prior work has often grouped maternal and fetal inflammatory responses together (Murphy et al., 1995; Grether and Nelson, 1997; Yoon et al., 1997; Wu and Colford, 2000; Rezaie and Dean, 2002; Polam et al., 2005; Shi et al., 2017). Using a large clinical cohort of extremely preterm infants, the Mir Lab has shown that this distinction matters: maternal inflammatory response reflects inflammation largely confined to the amniotic sac and nonvascular parts of the placenta, whereas FIR, identified by funisitis or chorionic vasculitis, signals that the fetus itself has mounted a systemic inflammatory reaction (Khong et al., 2016) which may be most relevant to brain development.

A prospective cohort of infants born before 29 weeks' gestation at Parkland Hospital, Dallas between 2018 and 2021 underwent brain MRI at 38–42 weeks (term-corrected) postmenstrual age as part of an established clinical protocol (Ibrahim et al., 2018). Placental histopathology was reviewed using Amsterdam Placental Workshop Group criteria that allow standardized and replicable placental assessment so that FIR could be staged by progression and graded by severity (Khong et al., 2016). Infant brain MRI abnormalities were scored using the Kidokoro system, which integrates regional measures of white matter, cortical gray matter, deep gray matter, cerebellar abnormalities, and a global brain abnormality score and has a demonstrated association with later neurodevelopmental outcomes (Kidokoro et al., 2013; Bonezzi et al., 2026). Importantly, MRI readers were blinded to clinical history, and discrepant scores were adjudicated by an independent third reader (Mir et al., 2025).

Among 141 extremely preterm infants, FIR was present in 59, or 42%, and most affected infants had advanced inflammation, with 46 of 59 classified as stage 2 or higher. FIR was associated with higher global brain abnormality scores at term-equivalent age, with the strongest regional associations in white matter and cerebellum. Increasing severity of FIR showed a dose-related relationship with worse MRI scores, extending beyond white matter to include cortical gray matter abnormalities. In multivariable models adjusting for gestational age, severe intraventricular hemorrhage, and 5 min Apgar score, FIR remained independently associated with abnormal global MRI scores. The association also persisted in the subset of infants without severe intraventricular hemorrhage, suggesting that FIR is not merely a proxy for hemorrhagic injury or lower gestational age (Mir et al., 2025).

Biologically, these findings fit with an emerging model in which fetal immune activation, including in the placental vasculature, initiates a cascade of immune-mediated injury (Romero et al., 1998; Klein and Gibbs, 2005; Patra et al., 2017; Jung et al., 2020). Fetal brain exposure to pro-inflammatory cytokines and other immune modulators may damage premyelinating oligodendrocytes, activate microglia, disrupt the BBB, and make the immature brain more susceptible to later postnatal insults (Burd et al., 2012; Kuypers et al., 2012). This "multiple-hit" framework is particularly relevant for extremely preterm infants, who often transition from an inflamed intrauterine environment into intensive care exposures that cause additional inflammation, including respiratory illness, prolonged ventilation, and sepsis (Yap and Perlman, 2020).

Clinical observations such as these that link early immune exposures to lifelong neurodevelopmental trajectories provide strong support for identifying placenta and brain biomarkers of risk. The placenta provides a biologic record of fetal inflammatory exposure and may help identify infants at heightened risk for altered brain development during intensive care, well before neurodevelopmental impairments become clinically apparent. Standardized placental examination paired with structured term-equivalent MRI scoring offers a practical path toward better risk stratification for preterm and other at-risk newborns, supporting a role for targeted surveillance, therapies aimed at modifying inflammation, and targeted early developmental intervention. The Mir lab findings also highlight an important concept: not all intrauterine inflammation carries the same implication for the fetus. The fetal vascular compartment appears to carry the critical signal. Future work should integrate placental assessment with cord blood cytokines and other inflammatory marker measurements, immune-cell phenotyping, advanced imaging methods, and longitudinal neurodevelopmental follow-up. Clinical cohort studies are a key first step in developing and targeting new therapies for infants shown to be at increased neurodevelopmental risk due to placental pathology.

Disruption of Placental Structure and Neurovascular Development by Inflammation Leads to Lifelong Neurological Disorders (Bonnin)

As important as clinical cohort studies are at identifying correlations between pathologies and outcomes, they cannot assess causal links or critical mechanisms involved in placental biology. While FIR syndrome associated with chorioamnionitis may increase neurodevelopmental risk, epidemiological studies have also linked other prenatal maternal exposures to infection, fever, and inflammatory events—especially during the first and second

trimesters—to elevated risks of neurological and psychiatric disorders in offspring (Knuesel et al., 2014). Models of MIA, a condition produced by maternal infection or inflammation during pregnancy, have begun to mechanistically address the question of whether the placenta is a crucial mediator of inflammatory signaling and therefore also a target for intervention. The Bonnin lab investigates how inflammatory signals cross protective fetal barriers, including the placenta and the BBB, to alter neurodevelopment.

During fetal life, there are two important biological barriers: the placenta and the fetal BBB. Similar to the placenta, the BBB regulates molecular exchange to the fetal brain and protects it from harmful substances. Yet during pregnancy these barriers are still developing and may be vulnerable to inflammatory disruption. Using rodent models, which allow real-time analysis of maternal, placental, and fetal physiology, maternal inflammation effects on placental signaling and BBB maturation have been examined.

One important line of investigation focuses on serotonin (5-HT), a neurotransmitter that also functions as a developmental signaling molecule. The placenta synthesizes 5-HT from maternal tryptophan and delivers it to the fetal forebrain during early gestation (Bonnin et al., 2011). This placental 5-HT contributes directly to the formation of fetal neural circuits. Mild maternal inflammation induced by low-dose poly(I:C), a viral mimetic, increases placental 5-HT production and alters 5-HT levels in the fetal forebrain. These changes disrupt serotonergic axon growth and circuit organization in the fetal brain during a critical developmental window (Goeden et al., 2016).

These experiments also demonstrate that extracellular 5-HT can inhibit serotonergic axon outgrowth in vitro through the serotonin receptor signaling pathways. Additional ex vivo fetal perfusion experiments reveal that 5-HT originating from the placenta can cross the fetal BBB and reach the forebrain parenchyma. Importantly, BBB permeability varies across different regions of the fetal brain, suggesting that BBB maturation is not uniform and may selectively influence vulnerability to circulating molecules such as 5-HT. Together, these findings support the idea that maternal inflammation indirectly alters fetal brain wiring through placental 5-HT dysregulation.

The second major research theme in the Bonnin lab addresses severe maternal inflammation and the mechanisms underlying its effects in the fetal brain. MIA triggered by high-dose poly(I:C) disrupts BBB structure and function in fetal mice, producing increased permeability, altered endothelial cell–pericyte coupling, and inflammatory activation of microglia. The COX2/mPGES1/PGE2 inflammatory signaling pathway has been identified as a key mediator of these effects (Zhao et al., 2022). Severe inflammation elevates prostaglandin production in the placenta and fetal brain, particularly prostaglandin E2 (PGE2), which acts through EP2 and EP3 receptors expressed on endothelial cells, pericytes, and microglia. Prostaglandins released from placental cells into fetal circulation contribute to BBB breakdown and neurovascular dysfunction (Horackova et al., 2026). Organotypic slice cultures and imaging studies show that PGE2 rapidly reduces endothelial–pericyte interactions and increases microglia–pericyte contact, potentially promoting vascular instability and inflammation.

Long-term studies in mice reveal that prenatal inflammation has persistent consequences extending into adulthood and aging. Offspring exposed to severe maternal inflammation exhibit chronic BBB leakage, activated perivascular microglia, altered cerebrovascular integrity, and behavioral abnormalities (Zhao et al., 2022). Some of these changes resemble features associated with accelerated brain aging. Notably, interventions targeting inflammatory pathways, including COX2 inhibition and microglial depletion-repopulation strategies, partially normalize these abnormalities, suggesting possible therapeutic opportunities.

Overall, these findings demonstrate that the placenta is an active regulator of fetal neurodevelopment through pathways involving serotonin, prostaglandins, immune signaling, and BBB maturation. Varying severity of maternal inflammation may produce distinct developmental trajectories ranging from subtle neural circuit miswiring to chronic neurovascular dysfunction and neurodegeneration later in life. Thus, even when the placenta is long gone, it may be shaping lifelong brain vulnerability in subtle or profound ways.

Placental Neuroactive Steroids Shape Brain Development: Influence of Sex and Therapeutic Potential (Vacher)

The placenta is not only an immune regulator but also the first fetal endocrine organ, producing neuroactive hormones long before the brain can do so for itself. Because placental hormone exposures occur while neural lineages, neuronal circuits, and long-range connectivity are being established, even transient shifts in placental endocrine function could alter developmental trajectories and long-term behaviors. Work in the Penn lab has focused on one key placenta-derived regulator of neurodevelopment, allopregnanolone (ALLO; 3α,5α-tetrahydroprogesterone). ALLO is synthesized from progesterone in the placenta at high levels in mid-to-late gestation (Pluchino et al., 2016; Vacher et al., 2021) in humans and rodents. It is a potent positive allosteric modulator of GABA-A receptors (Purdy et al., 1990; Lambert et al., 2003). In the developing brain, modulating GABAergic signaling does not only regulate neurotransmission strength and brain activity, but it also shapes proliferation, migration, synaptogenesis, myelination, and the maturation of neural networks (Wang and Kriegstein, 2009; Tang et al., 2021). ALLO also exhibits nonglucocorticoid anti-inflammatory activity (Balan et al., 2019; Yilmaz et al., 2019; Balan et al., 2023; Balan et al., 2024; Bäckström et al., 2024), positioning it at an intersection between endocrine and immune regulation. Birth triggers an abrupt loss of placental ALLO with a subsequent rise in brain ALLO production but preterm delivery produces "premature neurosteroid withdrawal" that occurs before the brain synthesizes ALLO (Hirst et al., 2008; Kelleher et al., 2013; Brunton et al., 2014; Shaw et al., 2019). Thus preterm birth via placental loss could directly alter GABAergic tone, impair neuronal and glial development, and shift inflammatory signaling during sensitive developmental windows.

To mechanistically test this hypothesis, Vacher and colleagues established a mouse model of placental trophoblast-specific ALLO insufficiency (plKO; Vacher et al., 2021). In this model, the reduced placental ALLO is sufficient to decrease fetal brain ALLO levels and drive enduring, region- and sex-dependent neurobehavioral phenotypes. A particularly striking result is the male-specific emergence of ASD-relevant behaviors, including altered ultrasonic vocalizations in the first postnatal week and, by postnatal day 30 (P30), reduced sociability alongside increased repetitive/stereotyped behavior. The cerebellum—implicated in both motor and cognitive functions and strongly linked to ASD risk—shows especially pronounced effects. At P30, these offspring lacking placental ALLO display robust, sexually divergent alterations in cerebellar white matter: males exhibit

hypermyelination whereas females show hypomyelination. Multiple readouts converge on this developmental window, including dysregulation of myelin/oligodendrocyte gene programs, changes in myelin proteins, ultrastructural shifts in myelin thickness (increased in males, decreased in females), and diffusion MRI evidence of altered white matter microstructure (e.g., elevated fractional anisotropy in males). Importantly, these cerebellar anatomical phenotypes are developmentally dynamic—differences prominent at P30 can attenuate at later ages—supporting a stage-specific shift in myelin trajectory rather than a fixed endpoint. This timing matters because transient deviations in myelin maturation can still bias circuit refinement and program long-term behavior.

Mechanistic follow-up studies support an immune–glia pathway downstream of placental endocrine disruption. Placental ALLO insufficiency is accompanied by sex- and age-dependent inflammatory signatures in both placenta and brain, together with altered microglial states in the postnatal cerebellar white matter (Salzbank et al., 2025). Because microglia regulate developmental myelin remodeling (Pang et al., 2013; Hagemeyer et al., 2017; Wlodarczyk et al., 2017; Staszewski and Hagemeyer, 2019; Hughes and Appel, 2020; Kalafatakis and Karagogeos, 2021; Santos and Fields, 2021), shifts in microglial phagocytic activity provide a plausible link between prenatal endocrine perturbation and postnatal myelin phenotypes. Specific mechanisms—including SIRPα–CD47 signaling and prostaglandin signaling (PGE2/EP4) changes—have been implicated as regulators of myelin engulfment and sex-linked white matter alterations (Salzbank et al., 2025), suggesting that targeting these and other neuroimmune pathways might mitigate downstream effects of placental ALLO loss as well.

The sex differences in the response to placental ALLO insufficiency are striking as are the region-specific effects. In cerebral cortex, the plKO model reveals a distinct vulnerability profile: females, but not males, show selective deficits in somatosensory cortical pyramidal neurons and altered sensory processing (Bakalar et al., 2022), highlighting that the same placental endocrine perturbation can manifest differently across brain regions and sexes. These dissociations argue against a single, global-effect model and instead support the idea that placental ALLO sets sex-dependent developmental starting conditions for multiple neural programs.

Translational relevance is strengthened by human and organoid data. Preterm birth is associated with human brain alterations in sex-linked cerebellar myelination (Vacher et al., 2021) and corticogenesis (Lacaille et al., 2019; Bakalar et al., 2022) that parallel the phenotype of these mice with reduced placental ALLO. Human cortical organoids provide experimental leverage to isolate direct effects: ALLO promotes human interneuron maturation, while ALLO withdrawal partially reverses these gains, indicating that loss of ALLO itself can redirect inhibitory developmental trajectories (Lacaille et al., 2025). Together with mouse studies demonstrating causality, these convergent findings support placental ALLO as a mechanistically interpretable placenta-to-brain signal linking endocrine withdrawal to neuroimmune tone, neural maturation trajectories, and ASD-relevant behaviors.

Therapeutically, the ALLO pathway is pharmacologically tractable, with clear clinical precedent that neurosteroid/GABA-A modulation can be leveraged in humans: brexanolone (Zulresso; Powell et al., 2020) and zuranolone (Zurzuvae; Barnes et al., 2024) are FDA approved for postpartum depression, and the ALLO analog ganaxolone (Ztalmy; De, 2024) is FDA approved for seizures associated with CDKL5 deficiency disorder. However, these approvals do not extend to prenatal use or to prevention/treatment of ASD, and available preclinical data indicate that benefit is likely to be highly dose and timing dependent. The Penn lab has shown that prenatal ALLO replacement or a GABA-A agonist prevents male behavioral abnormalities in the plKO placental ALLO insufficiency model (Vacher et al., 2021); moreover, elevating ALLO in otherwise control embryos increased ASD-relevant outcomes—together highlighting a constrained developmental dose–timing window. Translation will therefore require precise definition of when, how much, and by what mechanism to engage this pathway, alongside identification of downstream, mechanism-specific targets (e.g., immune–glia pathways, GABA-A receptor subunits, and region-specific developmental windows) that enable safe intervention in placenta-associated neurodevelopmental impairments.

Brain Vascular Alterations in Offspring Following Maternal Preeclampsia (Escudero)

Some preterm birth occurs in the setting of other pregnancy illnesses that affect the placenta, complicating the role of placenta-to-brain signaling for offspring in these contexts. Preeclampsia is a new-onset hypertensive disorder of pregnancy, affecting ∼2–8% of US pregnancies (Ford et al., 2022), and this disease remains a leading cause of maternal and perinatal morbidity and mortality globally. Pregnancies affected by preeclampsia are increasingly seen as a significant risk factor for long-term neurodevelopmental, cerebrovascular, and cognitive disorders in offspring (Figueiro-Filho et al., 2017; Dachew et al., 2018; Maher et al., 2018; Gumusoglu et al., 2020; Bandoli et al., 2022; Korzeniewski et al., 2022; Srivastava et al., 2022; Escudero et al., 2023; Zhen Lim et al., 2023). And preeclampsia has fundamental placental abnormalities, including dysregulated immune, vascular, and hormonal functions. However, the biological mechanisms linking the adverse intrauterine environment and placental changes of preeclampsia to brain developmental dysfunction remain poorly understood. Work from the Escudero lab is demonstrating how preeclampsia-relevant conditions impact cerebrovascular development and brain function, focusing on brain angiogenesis, cerebral perfusion, BBB integrity, neuroinflammation, and cognitive outcomes.

Multiple mouse models have been used to simulate preeclampsia-relevant conditions, specifically through reduced uterine perfusion pressure (RUPP) and the administration of the nitric oxide synthase inhibitor L-NAME during gestation. Offspring from these preeclamptic models exhibited decreased brain angiogenesis and impaired brain perfusion on P5 (Cumsille et al., 2022; Lara et al., 2022; Troncoso et al., 2023; Troncoso et al., 2026). Similar outcomes are evident also in 2-month-old offspring from the RUPP model (Saffold et al., 2026).

To assess possible compromised brain autoregulation—an essential mechanism that maintains consistent cerebral blood flow despite fluctuations in blood pressure (Tiecks et al., 1995)—laser speckle contrast imaging demonstrated microcirculatory responses. Reduced adaptive responses to thermal stimuli were found in the brains of offspring from both the RUPP (Cumsille et al., 2022) and L-NAME (Cumsille et al., 2025) models, suggesting early signs of vascular stiffness or loss of physiological responsiveness. Notably, these vascular alterations showed sex-dependent patterns. Thus, female offspring demonstrated greater impairment in the RUPP model, whereas male offspring were more affected in the L-NAME model.

Mechanistically, reduced vascular density in the motor and somatosensory cortices was associated with lower circulating levels of vascular endothelial growth factor (VEGF) and placental growth factor (PlGF), as well as reduced VEGF receptor-2 (VEGFR2) signaling in brain endothelial cells in P5 offspring. Functional analyses revealed impaired migration, altered cytoskeletal organization, reduced filopodia formation, and defective angiogenic capacity in brain endothelial cells (Troncoso et al., 2023; Troncoso et al., 2026). Moreover, exciting yet unpublished preliminary results identify thrombospondin-1 (TSP-1) as a novel mediator of placenta–brain endothelial communication in preeclampsia. Thus, high levels of TSP-1 in plasma from umbilical cord and conditioned media derived from umbilical cord endothelial cells of preeclamptic pregnancies may be associated with impaired brain endothelial angiogenesis by disrupting VEGF/VEGFR2/AKT signaling pathways.

The most recent Escudero lab work showed BBB dysfunction at P5 and long-term cognitive dysfunction in adult offspring from the L-NAME model. Importantly, adult offspring had deficits in recognition memory and spatial learning, indicating that early placental and brain vascular disruption may be a substrate for persistent functional consequences across the lifespan (Troncoso et al., 2026). In agreement with these results, cerebrovascular dysfunction was also reported in adult offspring exposed to experimental preeclampsia, including increased BBB permeability and altered cerebral artery function, particularly in males (Esposito et al., 2026). Interestingly, maternal apocynin, an antioxidant, prevented BBB dysfunction in male offspring, highlighting oxidative stress as a potential therapeutic target.

Beyond vascular dysfunction, increasing evidence indicates that modeled preeclampsia impairs hippocampal neurogenesis, alters synaptic plasticity, generates abnormal glucocorticoid receptor expression, and causes cognitive deficits in adolescent and adult offspring (Liu et al., 2016; Zhu et al., 2016). More recently, male offspring were demonstrated to be particularly vulnerable in terms of oligodendrocyte maturation, myelination, and social and cognitive behavior deficits (Wu et al., 2025). Importantly, environmental enrichment during adolescence partially restored some structural and brain functional alterations in offspring exposed to preeclampsia-modeled pregnancies (Lu et al., 2023; Wu et al., 2025).

Emerging evidence supports the existence of a complex placenta–brain metabolic axis in preeclampsia. Metabolomic approaches demonstrated coordinated alterations across maternal brain, placenta, serum, and offspring brain tissues, including changes in lactate, tryptophan, and inflammation-associated metabolites (Xu et al., 2025). Systemic metabolic remodeling originating in placenta and resulting in tissue cross talk may further contribute to altered neurodevelopmental outcomes in offspring exposed to preeclampsia.

Collectively, these findings support that preeclampsia, a placental-deficient condition, induces an early neurovascular "imprint" in the offspring through inflammatory and antiangiogenic mechanisms that impair angiogenesis, BBB maturation, cerebral perfusion, and brain development. These alterations may increase susceptibility to later cognitive and neurological disorders, highlighting placenta–brain communication pathways as potential sources of biomarkers and therapeutic targets.

Maternal Wellbeing and the Placenta: Implications for the Developing Brain (Nichols)

One of the main functions of the specific cellular structure of the placenta and its highly vascular nature is to allow the transfer of oxygen from maternal to fetal circulation. Preeclampsia and other pregnancy complications that reduce placental perfusion can result in reduced fetal oxygen delivery. When oxygen delivery to the fetus through the placenta is impaired, it can lead to brain sparing, where the brain is prioritized over the fetal body (Giussani, 2016). However, even with blood flow being redirected to the brain, the cerebral cortex tends to be deprioritized in favor of the subcortical areas critical in keeping the fetus alive (Hernandez-Andrade et al., 2008). To examine the relationship of placental oxygenation to brain morphogenesis, Nichols and colleagues apply MRI protocols using transverse relaxation time, or T2*, to assess placental function and dysfunction for fetal oxygen delivery during human pregnancy (Sinding et al., 2016; Baadsgaard et al., 2023). T2* is directly related to tissue oxygenation through its sensitivity to deoxyhemoglobin, which shortens relaxation time; in the hypoxic placenta, this manifests as lower measures of T2* relative to healthy tissue. For example, in a sample of fetuses with and without intrauterine growth restriction, Sinding and colleagues (Sinding et al., 2016) showed reduced T2* values in the growth restricted group. Even in complication-free pregnancies, lower placental T2* values are associated with smaller cortical volumes, while subcortical volumes remain largely unaffected, demonstrating the sensitivity of the fetal brain to placental oxygenation (Nichols et al., 2024).

Many factors can affect placental oxygenation; pregnancy complications such as intrauterine growth restriction, gestational diabetes, and preeclampsia have well-established negative effects (Soleymanlou et al., 2005; Ingram et al., 2017; Bianchi et al., 2021). Maternal stress, while not considered a pregnancy complication, is a widely experienced state (Woods et al., 2010) with downstream consequences for the health of both mother and fetus (Bansil et al., 2010; Papadopoulos et al., 2022). Chronic stress has damaging effects on tissue oxygenation throughout the body (Ostergaard et al., 2018) and well as potentially producing inflammation (Hantsoo et al., 2019). Maternal stress has been previously shown to affect fetal brain volumes and placental dysfunction has been proposed as the mechanism underlying this relationship (Bronson and Bale, 2016), but evidence of this pathway in humans is still lacking.

Nichols and colleagues investigated this link by collecting measures of maternal wellbeing, placental T2*, and fetal brain volumes in the third trimester in 100 healthy women with no pregnancy complications. The Perceived Stress Scale (Cohen et al., 1983) was used to measure maternal wellbeing. Participants were imaged with MRI at two time points in the third trimester with at least 2 weeks between scans. 2D multiecho stack placental images and single-shot fast spin echo anatomical fetal brain images were acquired. Placentas were segmented manually and brain regions were segmented using the Draw-EM pipeline (Makropoulos et al., 2016). Placental T2* values were calculated, and linear mixed-effects analysis on brain volumes was used to examine the moderating effect of T2* values on the relationship between perceived stress and brain volumes, controlling for fetal sex, gestational age, and brain hemisphere.

Within this sample, there was a significant interaction ($p < 0.05$, corrected using a false discovery rate) of T2* and perceived stress on volume of four cortical regions: the frontal lobe, the parietal lobe, the occipital lobe, and the superior temporal gyrus. No subcortical regions showed a moderating effect of T2*. In all regions, higher levels of maternal stress were linked to larger cortical brain volumes only when T2* values, representing placental oxygenation, were also low; when T2* levels remained high, brain volumes were unaffected by perceived stress.

This asymmetrical moderating effect of placental oxygenation on the relationship between maternal perceived stress and fetal brain volumes demonstrates the specificity of the relationship, with cortical regions being affected and subcortical regions being largely preserved. Importantly, if placental oxygenation remained high, the relationship between stress and brain volumes was not seen. The results of this study highlight the need for prenatal monitoring for factors beyond pregnancy complications and signs of clinical inflammation or endocrine dysfunction but rather emphasize the importance of maternal wellbeing screening and use of interventions to reduce perceived maternal stress.

Placental Impact on the Maternal Brain: A Multi-omic View of the Placenta–Maternal Brain Axis in Preeclampsia (Gumusoglu)

While significant evidence linking placental contributions to fetal and offspring brain outcomes has been presented, it should be recognized that placental factors may also impact maternal brain health and function. For example, preeclampsia (ACOG, 2020), discussed above in relation to fetal outcomes (Nomura et al., 2017; Gumusoglu et al., 2020), nearly triples maternal risk for perinatal anxiety and depression and predicts accelerated cognitive decline and dementia across the maternal lifespan (Fields et al., 2017; Miller, 2019; Srajer et al., 2022).

Preeclampsia results from impaired trophoblast invasion of the maternal uterine vessels leading to impaired uteroplacental blood flow. As noted above, this dysfunctional placenta then releases aberrant immune and angiogenic signals, not only into fetal circulation but primarily into maternal circulation (Conrad and Benyo, 1997; Wang et al., 2009; Tomimatsu et al., 2019; Varberg and Soares, 2021; Hu et al., 2022; Liu et al., 2022; Redman et al., 2022). How those signals reach and alter the maternal brain remains poorly understood (Gumusoglu, 2024). Current work in the Gumusoglu lab extends neuroplacentology beyond its neurodevelopmental framework into acute adult neuropsychiatric impacts which can also persist through the lifespan.

To examine placenta–maternal brain cross talk in preeclampsia, multi-omics strategies have been used in the chronic arginine vasopressin (AVP) mouse model. Elevated circulating AVP in early pregnancy is among the earliest predictors of preeclampsia in humans and is sufficient to phenocopy its hypertensive, immune, and renal features in pregnant mice (Santillan et al., 2014; Sandgren et al., 2015; Sandgren et al., 2018). In recent experiments, the Gumusoglu lab extended prior work in this AVP-based preeclampsia model in offspring brain (Gumusoglu et al., 2021) to examine the maternal brain—namely, its metabolomics, RNA sequencing, and behavioral phenotypes in late gestation and postpartum (Gumusoglu et al., 2025).

Peripheral metabolomics revealed minimal disruption overall by modeled preeclampsia, but the placenta showed robust multi-omic changes: 33 differentially expressed metabolites and 140 differentially expressed genes (DEGs), with joint-pathway analysis converging on purine metabolism. Among just those DEGs encoding secreted proteins from the placenta, enrichment analysis highlighted immune-inflammatory and vascular ontologies. Two candidates merited particular emphasis. *Cxcl17*, upregulated 5.4-fold in AVP placenta, regulates angiogenic factor expression in endothelial cells and monocytes and has been linked to cerebrovascular integrity (Lee et al., 2013). *C2cd4a* was upregulated 3.9-fold in AVP placenta and encodes endothelial-expressed NLF1, bridging inflammatory cytokine stimulation with vascular remodeling (Warton et al., 2004). These factors constitute plausible mediators in an immunovascular axis in preeclampsia bridging dysfunctional placenta and the maternal brain.

Late-gestation maternal brain RNA sequencing further revealed extensive gene suppression by modeled preeclampsia in both the hypothalamic paraventricular nucleus (PVN; 322 downregulated of 329 DEGs) and frontal cortex (113 downregulated of 114 DEGs). PVN pathways were enriched for neuronal system, oxytocin signaling, and calcium signaling, consistent with AVP's direct hypothalamic actions and prior evidence implicating oxytocin system disruption in perinatal mood disorders (Veenema and Neumann, 2008; Baracz et al., 2020; Schalla and Stengel, 2024). Cortical DEGs were enriched for complement, coagulation, and hemostasis pathways, mirroring the immunovascular signatures in the placenta and suggesting a shared upstream circulating driver of shared changes.

Functionally, dams that had experienced AVP-based preeclampsia modeling showed increased exploratory behavior and locomotion during late gestation without changes in depression-relevant or anhedonia measures. More consequentially, aged postpartum AVP dams demonstrated spatial memory deficits on Barnes maze associated with decreased hippocampal *Mmp9* expression. Mmp9 is required for hippocampal long-term potentiation and memory consolidation (Nagy et al., 2006) and its reduction aligns with growing clinical evidence of accelerated cognitive aging in those that have experienced preeclampsia (Srajer et al., 2022; Beckett et al., 2023; Escudero et al., 2023).

Collectively, these data position placental immunovascular dysfunction as a proximal driver of maternal brain changes in preeclampsia. Our findings implicate inflammatory and angiogenic placental secreted factors as determinants of maternal brain biology. Identifying these mediators opens a targeted route toward interventions that could attenuate both preeclampsia pathogenesis and its neuropsychiatric sequelae across the maternal lifespan.

Conclusions

The prenatal period is understood as foundational for offspring brain development and possibly for maternal brain adaptation. While brain changes during this period have been shown to be critical for later function, it is only recently that the brain has been understood to be directly shaped by a temporary organ, the placenta. Such sculpting is part of the fundamental nature of mammalian biology. The placenta can also play a role in brain disorders that have their onset during gestation.

Multiple laboratories are studying the links between placenta and brain in both animal models in which mediation and moderation of brain pathophysiology by placenta factors can be assessed directly and in clinical populations in which the implications of this novel biology can be demonstrated.

The endocrine connections between the placenta and fetal brain, including hormones, growth factors, and other signaling molecules have roles in specific processes of brain development and function, as demonstrated through work of the Bonnin lab, the Gumusoglu lab, and Vacher, Penn, and colleagues. In particular, because of the vascular nature of the placenta, the interaction of endothelial, blood oxygenation, and immune factors are prominent in brain structural formation, as demonstrated by the Mir lab, the Escudero lab, and Nichols and colleagues. The important role of inflammation and immune factors across all of the studies presented highlight this aspect of the

placenta–brain axis and suggest that different types of inflammation that occur in specific gestational windows will play a critical role in shaping specific neurodevelopmental impairments. Sex specificity is an additional aspect of these investigations of disease risk and also of the fundamental biology of the placenta; before sex-specific endocrine aspects of other tissues come online in development, the placenta has highly distinct biology in males and females which may contribute to sex differences in neurodevelopmental outcomes.

While discovery of placenta–brain interactions is revealing fascinating roles in normal development, multiple advanced molecular and imaging approaches are demonstrating the potential of leveraging placental biology for treating or preventing neurodevelopmental pathologies. As methods for probing and mapping complex biological interactions become even more sophisticated, the burgeoning field of neuroplacentology will yield additional knowledge and novel applications to a wide range of complex developmental disorders.

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