

## INVITED REVIEW

# Neuroactive steroid exposure impacts neurodevelopment: Comparison of human and rodent placental contribution

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## Abstract

The placenta is a fetal endocrine organ that secretes many neuroactive factors, including steroids, that play critical roles in brain development. The study of the placenta-brain axis and the links between placental function and brain development represents an emerging research area dubbed “neuroplacentology.” The placenta drives many circulating fetal steroids to very high levels during gestation. Recent studies have highlighted the critical role of placental steroids in shaping specific brain structures and behaviors. This review uses a cross-species framework to discuss the genomic factors, in-utero environmental changes, and placental conditions that alter placental steroidogenesis, leading to changes in early developmental trajectories relevant for psychiatric conditions such as autism, in a sex-linked manner.

## KEYWORDS

autism, maternal-fetal-placental unit, neurodevelopment, placenta, sex steroids

## 1 | THE PLACENTA-BRAIN AXIS AND THE EMERGING FIELD OF NEUROPLACENTOLOGY

The placenta remains a poorly understood organ, yet one that has life-long impact on both mother and child despite its transient existence. It is a multi-functional interface between mother and child that regulates gas exchange, nutrition, waste removal, and inflammatory exposures. As the first fetal endocrine organ to develop, it also synthesizes, transports, and metabolizes a vast array of hormones, including neuroactive steroids (e.g., estrogens, androgens, progestins) that enter both maternal and fetal circulation (reviewed in Ref. 1). Altered placental function can, in turn, modify fetal development, particularly the rapidly developing fetal brain.

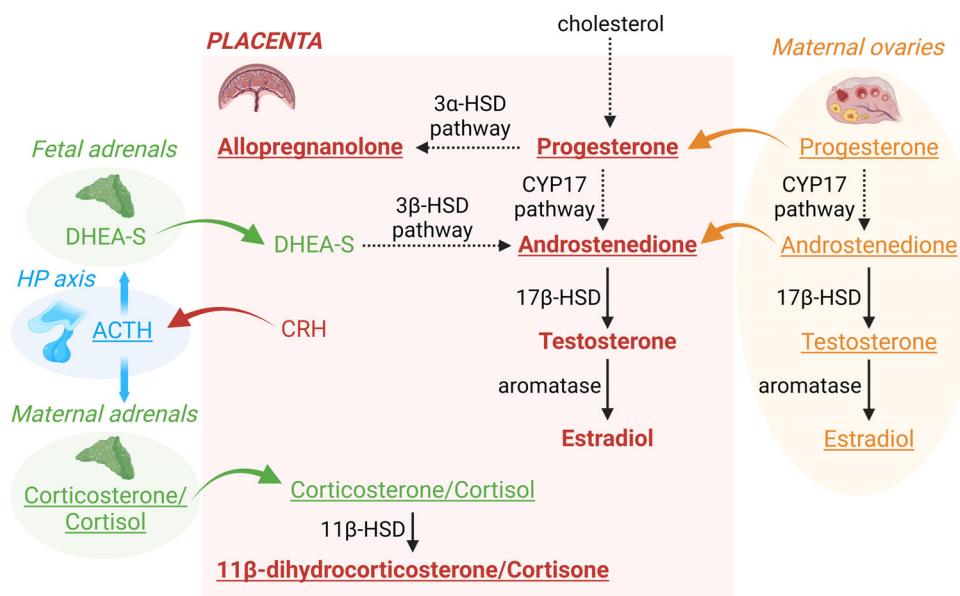
Neuroplacentology, the field linking placental pathology to neurodevelopment,<sup>2</sup> is expanding with human investigations support-

ing associations between placental pathology, hormone exposure, and neurodevelopmental risk in offspring.<sup>3-6</sup> New animal models that directly demonstrate the impact of placentally produced hormones on specific brain regions and behaviors are being investigated.<sup>7,8</sup> Here, we explore the current evidence from both human and preclinical rodent models supporting the hypothesis that placentally regulated exposures to sex steroids or their neuroactive derivatives (controlled by placental synthesis, transfer, or metabolism) have significant consequences for brain development.<sup>9</sup> A growing body of research demonstrates the capacity of sex steroids and their derivatives to shape specific brain regions and pathways that subsequently contribute to complex behaviors, including cognitive and social functions.<sup>8,10-16</sup>

Using cross-species comparisons allows for rapid preclinical modeling and testing in genetically tractable models such as rodents, but when linking placental development, sex steroids, and behavior, it is important to be aware of the limitations of these comparisons as

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**FIGURE 1** Overview of Steroidogenic Pathways in Human and Rodent Placenta: This figure illustrates the steroidogenic pathways discussed in this review. Color coding identifies the site of hormone production: placenta (red), ovaries (orange), adrenals (green), and hypothalamic-pituitary axis (blue). Hormones shown in bold emphasize their placental production. Hormones with underlined names denote conserved pathways between rodents and humans, while non-underlined hormones indicate pathways unique to primates. Straight arrows indicate enzymatic conversions (dotted arrows highlight multi-step conversions), with labels identifying the principal enzyme isoforms catalyzing each reaction. Curved arrows depict hormonal transport, while faded arrows represent regulation pathways. ACTH, adrenocorticotropic hormone; CRH, corticotropin-releasing hormone; CYP, cytochrome P450; DHEA, dehydroepiandrosterone; DHEA-S, dehydroepiandrosterone sulfate; HSD, hydroxysteroid dehydrogenase; HP, hypothalamic-pituitary.

well. Human and rodent placenta are both hemochorial, as the trophoblasts of both are directly bathed in maternal blood. However, their anatomical arrangement of cells differs, their specific developmental patterns of gene expression vary and production of steroids in pregnancy and by the placenta differs significantly.<sup>17-19</sup> In addition, developmental time points between mouse and human brain development during gestation 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.<sup>20</sup> Despite these differences, many functional properties are conserved between human and mouse, including dependence on an integrated maternal-fetal-placental unit, functional properties of placental hormone secreting cells (e.g., syncytiotrophoblasts), and specific hormone-responsive windows of prenatal programming.<sup>21-23</sup>

## 2 | HUMAN PLACENTAL STEROIDOGENESIS

Despite the stark differences in placental morphologies across species, one shared characteristic of trophoblast cells is their ability to synthesize or metabolize steroid hormones.<sup>24-29</sup> However, the extent to which the placenta produces steroid hormones, the variety of steroidogenic enzymes expressed, and the regulation of their synthesis can differ significantly (Figure 1).<sup>21,23,30</sup>

Anthropoid primates are among the few species that have a hemomonochorial placenta, characterized by a monolayer of syncytial

trophoblasts.<sup>31</sup> The invading trophoblast cells reach deep in the endometrium and over the course of pregnancy. They fuse with the maternal blood vessels, eventually bathing the placenta in the maternal circulation. Hormonally, the placenta of anthropoid primates is also characterized by a unique ability to synthesize chorionic gonadotropin (CG, hCG in humans) in the first half of gestation. The gene for this peptide is derived from a duplication and modification of the gene for the beta subunit of the luteinizing hormone (LH).<sup>32</sup> Interestingly, the human lineage has more duplication events for gonadotropin genes, leading to a greater number of functional hCG variants compared to other primates.<sup>32</sup> hCG regulates the first phases of placentation (adhesion, implantation, and differentiation), while the syncytiotrophoblasts are in the initial stages of invading the uterine wall. Following a peak in the late part of the first trimester, hCG catalyzes placental steroidogenesis, a process which is then maintained and accelerated by placental progesterone throughout the remainder of the pregnancy.

The fetal zone of the adrenal cortex begins to express cytochrome P450c17 (steroid 17 alpha-hydroxylase/17,20 lyase) by the 10th week of gestation, allowing for the synthesis of dehydroepiandrosterone (DHEA) and dehydroepiandrosterone sulfate (DHEA-S) from free cholesterol and progesterone.<sup>33</sup> This steroid is then fed back into the placenta (via hemochorial transfer), leading to the synthesis of androgens (androstenedione and testosterone) by the 3β-hydroxysteroid dehydrogenase (3β-HSD) enzyme and estrogens (estrone and estradiol) by the aromatase enzyme, which is expressed at very high levels in the syncytiotrophoblasts.<sup>34</sup> The placenta is the

primary source of estrogens during pregnancy, as indicated by higher levels of estrogens in the retroplacental space than in the maternal peripheral vein or umbilical vein/arteries.<sup>33,35</sup> In the second half of pregnancy, increased placental expression of the cytochrome CYP17A1 gene occurs, providing an additional “boost” to the levels of sex steroid hormones until term.<sup>36,37</sup>

The maternal and adrenal axes are further enhanced by another primate-specific adaptation of placental signaling: the synthesis and release of placental corticotropin-releasing hormone (CRH).<sup>38</sup> This potent hormone recruits the hypothalamic–pituitary–adrenal (HPA) and hypothalamic–pituitary–gonadal (HPG) axes of the mother and fetus, stimulating the release of adrenocorticotropic hormone (ACTH) by the pituitary and leading to positive feedback and the upregulation of steroidogenesis throughout pregnancy.<sup>39</sup> Comparative studies between primates indicate that prenatal steroidogenesis is particularly enhanced in humans. Humans have a much higher peak level of estrogens during pregnancy than chimps, orangutans, and gorillas.<sup>40,41</sup> The human placenta can be considered to have adapted into a “steroidogenic engine” that utilizes the uniquely deep invasion of the trophoblasts to integrate the maternal and fetal steroidogenic capacities.<sup>33,38</sup> However, these adaptations may confer increased risk for pregnancy-related complications. The human placenta is more invasive than in other primates, leading to higher prevalence of vascular complications.<sup>42</sup> Direct links between human-specific placental endocrine processes and brain development are under active investigation.

### 3 | RODENT PLACENTAL STEROIDOGENESIS

The placenta of most myomorph rodents, such as rats and mice, has three layers of trophoblasts, making it a hemotrichorial placenta. It consists of an outer trophoblast layer that is directly immersed in maternal blood (the junctional zone), along with two inner layers of syncytial trophoblasts (the labyrinth zone).<sup>43</sup> The junctional zone contains trophoblast giant cells that produce steroid hormones.<sup>44</sup> Unlike humans, rodent gestation requires ongoing collaboration between the ovaries and placental endocrine cells to maintain the production of progesterone and estradiol throughout pregnancy<sup>18,45</sup> (Figure 1).

In rodents, 3 $\beta$ -HSD initiates progesterone synthesis in maternal post-implantation decidual cells until the giant trophoblast cells of the placenta take over from embryonic day (E) 7.5–8.5 to mid-gestation.<sup>30,46–48</sup> In the mature placenta, 3 $\beta$ -HSD is no longer expressed so the ovaries remain the primary source of pregnancy-supporting progesterone.<sup>45,49</sup> Additionally, the rodent placenta does not express P450 aromatase and thus cannot convert androgens to estrogens.<sup>50,51</sup> Instead, it utilizes 17-hydroxylase activities to synthesize de novo androgens, which are then converted to estrogens by ovarian P450 aromatase.<sup>52,53</sup> Like humans, placental glucocorticoid metabolism in rodents is regulated by 11 $\beta$ -hydroxysteroid dehydrogenase type 2 (11 $\beta$ -HSD2), which acts as a fetal protective barrier against maternal glucocorticoids—which increase during gestation—by rapidly converting active corticosterone (cortisol in humans) into inert metabolites.<sup>54</sup> In contrast to primates, rodent placentae do not

express CRH.<sup>55–57</sup> It is hypothesized that placental production of CRH evolved in primates to stimulate fetal ACTH release and adrenal steroidogenesis, leading to sufficient DHEA and DHEA-S production and subsequent sex hormone synthesis.

### 4 | ALTERED PLACENTAL STEROIDOGENESIS IN HUMAN NEURODEVELOPMENT

Accumulating evidence from studies in developmental neuroscience and psychology suggests that perinatal steroid levels, particularly androgens, are associated with the development of many human faculties, such as language development,<sup>58</sup> empathy and “mind-reading,”<sup>12</sup> and non-verbal social communication and behavior.<sup>11,59–61</sup> The sex-specific trajectories of vocabulary acquisition<sup>62</sup> and the development of theory-of-mind and other socio-cognitive milestones<sup>63–65</sup> may, therefore, be attributable in part to prenatal androgen exposure. Non-human animal models have demonstrated that manipulation of testosterone levels can generate sex-dependent changes in behavior. Across species, exposing developing female animals to testosterone prenatally masculinizes social behaviors that are typically sexually dimorphic. For example, female monkeys that are prenatally exposed to exogenous testosterone display more male-typical play compared to unexposed females.<sup>65,66</sup> On the other hand, developing males who are exposed to antagonists for the androgen receptor exhibit reduced male-typical play behavior. These findings parallel some human observational studies. By 12 months of age, children show sex-typed play behavior patterns with distinct preferences in toys<sup>67–69</sup> and playmates<sup>70,71</sup> and prenatal testosterone exposure is associated with male-typical play behavior.<sup>11,59,60,72,73</sup>

Emphasis has been placed on the role of prenatal androgen exposure in driving the development of empathy and social connections in humans. Brain regions that have been implicated in empathy and emotion recognition and regulation, such as the amygdala, right temporoparietal junction, the fusiform gyrus, and the medial prefrontal cortex, have sexually dimorphic structural and functional properties that have the potential to be shaped by the organizational effects of sex hormones.<sup>10,74,75</sup> Within 30 min of birth, human neonates demonstrate preferential looking towards social stimuli (face-like images versus non-face-like images).<sup>76</sup> Sex difference emerges in the first 24 h after birth: Female neonates spend significantly more time gazing at a face-like image compared to a non-face-like image, whereas male neonates exhibit preferential looking towards non-face-like stimuli.<sup>64</sup> Thus, even newborn infants have a proclivity for social interaction and the early emergence of a sex differences in preferential looking toward social stimuli independent of social learning or modeling suggests potential prenatal influences.

Prenatal androgen exposure may alter later behavior and cognition responses as well. By 12 months of age, higher frequency and duration of eye contacts are associated with lower testosterone levels in amniotic fluid during mid-pregnancy, especially in boys.<sup>61</sup> Similarly, higher levels of amniotic fluid testosterone are associated with a more restricted vocabulary size in toddlerhood.<sup>77</sup> In middle childhood,

children's ability to accurately assign an emotion to images of the eye region of a face (Eyes-C) and scores on the child version of the Empathizing Quotient are negatively correlated with testosterone in amniotic fluid.<sup>12</sup> However, other indicators of empathy, such as the use of affective state terms, have not been shown to relate to amniotic fluid levels of testosterone.<sup>12</sup>

## 5 | PRENATAL STEROID EXPOSURES AND AUTISM RISK

There is growing evidence to suggest that disruptions in placental steroid regulation and therefore, fetal exposure to aberrant levels of steroid hormones, may contribute to the pathophysiology of certain neuropsychiatric conditions, including autism.<sup>78,79</sup> Autism refers to an umbrella of neurodevelopmental conditions that share general features, including difficulties with social interaction and communication, as well as restricted interests and repetitive behaviors.<sup>80</sup> It is frequently accompanied by atypical patterns of language development, sensory hyper/hypo-sensitivities, and varying levels of disability. A large percentage of the variance in autism likelihood and autistic traits can be attributed to genetic variants that can be both rare and common.<sup>81</sup>

To account for the consistent sex bias in autism prevalence, as well as “male-type” shifts in behavior, brain structure, and anatomy, the prenatal steroid theory of autism was put forward and evaluated in various studies and independent cohorts.<sup>82</sup> Abnormal steroidogenic activity during pregnancy may alter the development and organization of hormone-sensitive brain regions that contribute to sensory processing, emotional regulation, cognition, and social behavior, all of which being affected in individuals with autism.<sup>14,59,83</sup> Notably, steroid hormones may primarily act early in gestation, as androgens measured at birth in cord blood (testosterone, androstenedione, and dehydroepiandrosterone) are not associated with autistic traits.<sup>84</sup>

The first studies reported a correlation between amniotic testosterone and measures of autistic traits in children during infancy and childhood.<sup>85,86</sup> More recently, higher levels of maternal testosterone during the second trimester were also found to be associated with more autistic traits.<sup>87</sup> A case-control comparison in males also found that several steroid hormones produced by the placenta, including androgens, were elevated in autism when these were examined together as a prenatal “steroidogenic factor.”<sup>88</sup>

Epidemiological studies are also in line with these clinical findings, with polycystic ovarian syndrome (PCOS) in the mother increasing the likelihood of her child having autism.<sup>89-93</sup> PCOS is an endocrine condition that affects an estimated 5%–10% of the population and is characterized by polycystic ovaries, infertility and ovulatory dysfunction, and hyperandrogenism.<sup>93-96</sup> Pregnant women with PCOS have been reported to have higher levels of circulating testosterone and may feature atypical steroid production by the placenta during pregnancy compared to pregnant women without PCOS.<sup>95-97</sup> In addition, women with PCOS have been shown to have higher baseline levels of allopregnanolone<sup>98</sup> but may actually show reduced sensitivity to its

effects on GABAergic signaling.<sup>99</sup> Though the underlying mechanism is not well-understood, studies have found a relationship between maternal PCOS and increased likelihood for neurodevelopmental conditions, including autism.<sup>92,95,100-102</sup> PCOS, itself, is now recognized as a condition of neurodevelopmental significance, as the children of mothers with PCOS are more likely to have PCOS themselves, but also to feature a varied combination of neuropsychiatric traits and mental health needs.<sup>89</sup> In two matched case-control studies, the odds of a child being diagnosed with autism was approximately 60% higher if their mother was diagnosed with PCOS compared to children whose mothers did not have PCOS.<sup>91,93</sup>

Hypertensive disorders of pregnancy, including gestational hypertension, preeclampsia, eclampsia, and HELLP (hemolysis, elevated liver enzymes and low platelets) syndrome, offer another example of a clinical condition associated with both maternal hyperandrogenism during pregnancy and increased likelihood for autism in the next generation.<sup>103-107</sup> Since pre-eclampsia is typically not diagnosed until mid-to-late gestation, the majority of studies investigating steroid levels in individuals with preeclampsia include samples collected near the time of delivery. As a result, there is limited data on first and second trimester steroid levels in pregnancies that are later complicated by preeclampsia. One retrospective frequency matched cohort study found that maternal testosterone levels sampled earlier in pregnancy (16–21 weeks gestational age) were higher among women with preeclampsia who carried a female fetus, but not a male fetus.<sup>102</sup> Further, compared to normotensive pregnancies, in which maternal testosterone levels do not typically differ by the sex of the fetus, women with preeclampsia who carry a male fetus have higher testosterone levels compared those carrying a female fetus.<sup>108</sup>

In recent years, prenatal estrogens have also been implicated in autism and related traits. A “steroidogenic factor” linked to autism risk in the Danish Biobank cohort was found mainly to be driven by the effects of estrogens, such as estradiol.<sup>78</sup> Following this study, the same estrogenic effect on autism was found when assessing maternal plasma in independent cohorts in Utah,<sup>109</sup> and Cambridge.<sup>110</sup>

Estrogens are synthesized from androgens via aromatization in a single, enzymatic step. In humans, the placenta is the main site of aromatization during prenatal development. The human aromatase gene features multiple tissue-specific promoter sequences, which evolved in the primate lineage.<sup>111</sup> These include a placenta-specific promoter and a brain-specific promoter, which are absent in rodents.<sup>112-116</sup> Aromatase expression in the human brain is high particularly during development,<sup>117</sup> suggesting that local androgen to estrogen conversion may be shaping neural development.<sup>118</sup>

Interpretation of human cohort studies is limited however by the wide range of normal steroid levels in the general population plus study differences in cohorts evaluated, methods and timing of steroid measurements and study design.<sup>62</sup> Controversy continues to surround the complex link between prenatal steroid exposure and specific human behaviors, including autism risk. Reductionist human models, such as human-induced pluripotent stem cell (iPSC)-derived brain organoids, may provide greater mechanistic insights soon.<sup>119</sup>

Recent human placental analysis has begun to focus on the associations between neurodevelopmental traits (e.g., in attention or sociability) and placental gene expression, microRNA expression,<sup>120</sup> and signaling by extra-cellular vesicles.<sup>3,121</sup> An overlap in genomic patterns between the brains of autistic people (profiled post-mortem in donors) and the placentas of autistic people in independent cohorts has been identified.<sup>122</sup> Interestingly, sex differences in placental gene expression and production of specific factors, such as placenta growth factor (PGF), are significant mediators of sex differences in autistic traits in both general populations and rare genetic syndromes associated with autism.<sup>4,123</sup> Similar overlap between genes and microRNAs expressed in placenta and linked to placental complications have recently been described as mediators of schizophrenia, a late appearing neurodevelopmental disorder.<sup>5,124</sup> Connecting placental steroidogenic gene expression and steroid levels in human placenta with the genomics of neurodevelopmental conditions is a next step in understanding the genomic and hormonal interplay that may shape human behaviors.

Alongside these biological considerations, it is important to recognize that females often face several barriers to autism diagnosis. These barriers include differences in symptom presentation, with females showing fewer social difficulties and more internalized symptoms like anxiety,<sup>125</sup> and the development of compensatory behaviors to mask their traits.<sup>126</sup> Additionally, gender biases in diagnostic criteria and a lack of awareness among parents and clinicians may further contribute to underdiagnosis of females, falsely accentuating autism's sex bias.<sup>127</sup>

## 6 | PLACENTAL STEROIDS AND NEURODEVELOPMENT IN RODENT MODELS

New data emerging from genetic mouse models has started to shed light on the pivotal role of placental neuroactive steroids in shaping cognitive brain circuits.<sup>128</sup> While expression of estrogens and androgens differ in mouse and human placenta, progesterone and its derivatives are highly conserved.<sup>129</sup> A key example is the neuroactive steroid allopregnanolone, a  $3\alpha,5\alpha$ -progesterone metabolite abundantly produced by the placenta in both humans and rodents.<sup>130–133</sup> Allopregnanolone is synthesized from progesterone through the sequential action of  $5\alpha$ -reductase ( $5\alpha$ -R), which reduces progesterone into dihydroprogesterone (DHP), and  $3\alpha$ -hydroxysteroid dehydrogenase ( $3\alpha$ -HSD), which converts DHP into allopregnanolone.<sup>130–134</sup> While allopregnanolone can be made de novo in the adult brain,<sup>133,135</sup> its remarkably high level in the fetal brain results primarily from placental production.<sup>8,136–138</sup> In mice, the *akr1c14* gene, encoding  $3\alpha$ -HSD (the last-step enzyme in allopregnanolone synthesis), is expressed up to 60 times more in the placenta than in the fetal brain.<sup>8,139,140</sup> Allopregnanolone primarily acts as a potent positive allosteric modulator of GABA<sub>A</sub> receptors (GABA<sub>A</sub>Rs),<sup>139,141,142</sup> prolonging the opening of the GABA-gated Cl<sup>-</sup> channel by binding to specific receptor sites.<sup>139,142–144</sup> In the mature brain, this positive modulation of GABA<sub>A</sub>R activity produces cell hyperpolarization,

resulting in sedative, anxiolytic, anesthetic, and anticonvulsant effects.<sup>144,145</sup> However, in immature neural cells, this can lead to cell depolarization and enhanced neuronal excitability<sup>146</sup> due to a reverse chloride gradient.<sup>147</sup> This response is involved in regulating developmental cell proliferation,<sup>148</sup> including neurogenesis.<sup>146,148–151</sup>

Allopregnanolone activation of other receptors besides GABA<sub>A</sub>Rs can also contribute to its diverse effects. While allopregnanolone is inactive at the nuclear progesterone receptor (PR) at physiological concentrations,<sup>152</sup> it can activate membrane progesterone receptors  $\delta$  (mPR $\delta$ ), producing anti-apoptotic effects,<sup>153</sup> or be intracellularly oxidized into  $5\alpha$ -DHP, an agonist of the PR, potentially leading to PR-mediated responses.<sup>154</sup> Allopregnanolone also exhibits anti-inflammatory properties through at least two mechanisms: activating pregnane X receptor (PXR)-dependent pathways<sup>155,156</sup> and inhibiting TLR4 and TLR7-signaling pathways.<sup>157–159</sup> More speculatively, allopregnanolone has been suggested to regulate the activity of the dopamine D1 receptor<sup>160</sup> and NMDA receptors,<sup>161</sup> though the directness of these effects remains unclear.

In a conditional knockout mouse model (referred to as pIKO), the trophoblast-specific deletion of *akr1c14* leads to a two-fold reduction in allopregnanolone levels in the placenta and subsequently in the fetal brain.<sup>8</sup> The pIKO mice exhibit alterations in gray and white matter development, as well as long-term behaviors resembling autism-like features, with significant regional and sex-linked differences. Specifically, during embryonic stages, placental allopregnanolone insufficiency disrupts neurogenesis and gliogenesis. Cortical plate neurons destined for the upper layers of the primary somatosensory cortex (S1) are impaired,<sup>7</sup> while oligodendrocyte (OL) progenitor cell proliferation in the cerebellar white matter is enhanced.<sup>8</sup> As development progresses from the postnatal period to adolescence, sex-linked differences emerge. In female pIKO brains, there is a persistent reduction in pyramidal neuron density in the upper layers of the S1 cortex and a reduced maturation rate of the OL lineage in the cerebellum, resulting in cerebellar axon hypomyelination at adolescence. Conversely, male pIKO brains normalize pyramidal neuron density in the S1 cortex but maintain a high progression rate within the cerebellar OL lineage, leading to cerebellar hypermyelination at adolescence. These sex-linked cellular alterations correlate with behavioral impairments: somatosensory deficits in pIKO females and decreased sociability associated with motor stereotypies in pIKO males. Both male and female pIKO phenotypes align with autism-like features at the cellular or behavioral level<sup>162–169</sup> and are considered “autism-like” behaviors in multiple genetic mouse models.<sup>170,171</sup> The regional and sex-linked changes resulting from placental allopregnanolone insufficiency not only underscore the global impact of placental endocrine function on long-term neurodevelopmental outcomes, but also emphasize the importance of recognizing and investigating distinct sex-linked differences to better target therapeutic approaches.

Treating pIKO mice with allopregnanolone during fetal life rescues autism-like behaviors in males, indicating that the neurobehavioral outcomes resulting from placental allopregnanolone insufficiency are amenable to pharmacological intervention.<sup>8</sup> However, in control littermates with normal placental allopregnanolone

production, excess in utero exposure to the steroid also increases the likelihood of autism-like behaviors in males.<sup>8</sup> This suggests in utero exposure to allopregnanolone beyond the physiological range may contribute to autism.

The significance of placental allopregnanolone levels likely extends to humans. Humans have at least four isoforms for the enzyme that produces allopregnanolone, compared to just one in rodents,<sup>172</sup> complicating placental assessments. However, allopregnanolone levels in humans are associated with neuropsychiatric disorders, specifically with post-partum depression in women<sup>173</sup> and “post-finasteride” syndrome in men (a newly described finasteride side effect that results in depression).<sup>173</sup> More recently, a study of 21 autistic males found that the serum allopregnanolone levels were negatively correlated with restricted and repetitive behaviors.<sup>13</sup> Allopregnanolone's impact on the excitatory/inhibitory ratio in the brain and potential for such changes to contribute to neurodevelopmental conditions such as autism highlights that need for mechanistic studies in mice in parallel with human investigations.<sup>13,174–176</sup>

## 7 | FUTURE AREAS FOR INVESTIGATION

Combining human studies showing statistical associations between in-utero neurosteroid exposure and human behaviors with breakthroughs provided by animal models is lending strong support to the idea that a number of placentally regulated sex steroids can alter brain development long term. To harness this knowledge for diagnostic or therapeutic use will require understanding of the windows of time during which these hormones can change brain cells or circuits, careful measurement of hormone levels across development in physiological and pathological conditions, and identification of the molecular mechanisms through which these hormones exert their influence. Additional cutting-edge research using human brain organoids exposed to specific combinations of steroids will begin to untangle the cellular mechanisms that may underlie these changes. Finally, integrating a growing body of genomic data available from next-generation sequencing technologies with clinical phenotypes and hormone patterns may reveal new links between placental steroids and neurodevelopment.

### AUTHOR CONTRIBUTIONS

**Claire-Marie Vacher:** Writing – review and editing; writing – original draft; conceptualization; funding acquisition. **Alex Tsompanidis:** Writing – review and editing; writing – original draft; conceptualization; funding acquisition. **Morgan R. Firestein:** Writing – review and editing; writing – original draft; conceptualization; funding acquisition. **Anna A. Penn:** Writing – review and editing; writing – original draft; conceptualization; funding acquisition.

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The authors declare no conflicts of interest.

### PEER REVIEW

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### DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

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