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Review article

Frank Beach Award Winner - The future of mental health research: Examining the interactions of the immune, endocrine and nervous systems between mother and infant and how they affect mental health

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ABSTRACT

Pregnancy and the postpartum period are periods of significant change in the immune and endocrine systems. This period of life is also associated with an increased risk of mental health disorders in the mother, and an increased risk of developmental and neuropsychiatric disorders in her infant. The collective data described here supports the idea that peripartum mood disorders in mother and developmental disorders in her infant likely reflects multiple pathogeneses, stemming from various interactions between the immune, endocrine and nervous systems, thereby resulting in various symptom constellations. In this case, testing the mechanisms underlying specific symptoms of these disorders (e.g. deficits in specific types of learning or anhedonia) may provide a better understanding of the various physiological interactions and multiple etiologies that most likely underlie the risk of mental health disorders during this unique time in life. The goal here is to summarize the current understanding of how immune and endocrine factors contribute to maternal mental health, while simultaneously understanding the impact these unique interactions have on the developing brain of her infant.

1. Introduction and significance

Maternal and fetal medicine are an important component of Women's Health, and this particular niche of medicine has continue to gain increased attention in recent years. In spite of that, maternal and fetal health outcomes have not improved in the United States in recent years. The Center for Disease Control (CDC) National Vital Statistics Reports indicate an increased rate of pre-term births, which rose to nearly 10% of all births in 2017 (Centers for Disease Control, 2018). They also report an increase in the number of infants with significantly low birth weights for the third year in a row, rising to nearly 8.2% of all live births in 2017. They also report that only 75% of women in the United States begin prenatal care in the first trimester, while nearly 25% of women don't begin any form of prenatal treatment until the second or third trimesters of pregnancy, if at all (Centers for Disease Control, 2018). Ultimately, infant mortality in the United States is high for a developed nation, as the CDC reports that 23,000 infants died in the United States in 2016 alone. These data clearly highlight that as a nation, we can do better. The goal of maternal and fetal medicine is that both mother and infant get the necessary assessment and care related to nutrition, environmental factors, infection, stress, or other conditions that increase the health risks for mother and infant throughout gestation and into the postpartum period. The Significance: *It's time that maternal and fetal medicine come to the forefront, because it is also now recognized that a lack of appropriate maternal-fetal care can increase the risk of negative mental health outcomes in both mother and infant.*

In 2013, Drs. Insel and Landis from the NIH wrote an important perspective on our progress and future in mental health research (Insel and Landis, 2013). They indicated that many neuropsychiatric disorders "*begin early in life*" and thus are the "*chronic diseases of the young*" that "*have become the largest source of years lived with disability*". We interpret "early in life" as the prenatal and the immediate neonatal or postpartum periods, and as such, these are sensitive periods of life for the infant *and* mother that should become an important consideration in our understanding of the etiology of mental health disorders. For example, pregnancy and the postpartum period is associated with an increased risk of depression and anxiety in 10–15% of mothers (Sherer et al., 2018). Moreover, the prevalence of developmental disorders, including autism, schizophrenia, generalized pervasive developmental disorders, and even learning disabilities in the United States is 13.87% (Boyle et al., 2011; Scott et al., 2016). The primary risk factors for developmental disorders include inadequate prenatal care, complications during pregnancy, maternal mental illness, early emotional deprivation, and in utero exposure to illness or toxins (Scott et al., 2016). Despite their prevalence and severity, the etiology of these various disorders are not well understood. **In our lab, we hypothesize that**

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interactions between the endocrine, immune and nervous system of mother and infant have an important impact on the risk of neural and psychiatric disorders in the offspring as well as the mother. Here we explore the evidence in support of this hypothesis with the goal of increasing awareness of specific issues in the field of mental health research that require further attention and additional research. We also discuss possible criteria for effective diagnosis, as well as mechanisms and risk factors associated with mental health outcomes in the mother and infant.

2. Part 1. Pregnancy is a unique period of immunological change in mother that has been understudied in the context of mental health

During pregnancy, a mother's immune system undergoes a number of important changes that begin at the moment of conception and continue through parturition. These changes in immune function are initiated by the cellular interactions at the placenta and the decidua of the uterus. They are maintained by elevated levels of pregnancy hormones, including progesterone and estrogens, and they are tightly controlled throughout pregnancy such that minor perturbations in immune function can affect the success of the pregnancy (Craenmehr et al., 2016; Salamonsen et al., 2016; Song and Shi, 2014). The immune system of the mother changes its function to accommodate the embryo for implantation, growth, development and maturation of the new infant, but this can also significantly contribute to the mother's health, both pre- and postpartum (Estes and McAllister, 2016; Harmon et al., 2016; Moffett and Loke, 2006). As a result of these changes in immune function, the induction of classical (Th1/M1) pro-inflammatory immune molecules, such as Interleukin (IL)-1β or Tumer Necrosis Factor (TNF)-α, are decreased over the course of gestation while a unique composition of alternate (Th2/M2) immune molecules are expressed in response to immune challenges (e.g. IL-4, IL-6, Arginase 1, and IL-10). The difference between these classical (Th1/M1) and alternative (Th2/M2) immune phenotypes results in very distinct profiles of immune activation in response to a challenge during pregnancy (Sherer et al., 2018). Thus, the consequences of this immunomodulation during pregnancy are significant. For example, late pregnancy is associated with increased severity, complications and mortality following various types of infections, both viral and bacterial, in humans and in rodent models (Klein et al., 2012; Robinson and Klein, 2012; van Riel et al., 2016). As a result, the immunomodulatory effects of pregnancy directly contribute to an overall female-bias in susceptibility to infection compared to males.

Pregnant women are also more susceptible to stress, anxiety, and mood-related disorders during pregnancy and the postpartum period (Cox et al., 1982; Faisal-Cury et al., 2008; Harris, 1994; M'baïlara et al., 2005; O'Hara et al., 1990; Raison and Miller, 2017; Wisner et al., 2013). It is thought that this vulnerability is the result of hormones, including estrogens, progestins, and cortisol that increase dramatically during pregnancy and drop precipitously postpartum (Corwin and Pajer, 2008; Galea et al., 2001; Harris, 1994; Hendrick et al., 1998; "NIMH Postpartum Depression Facts", n.d.; Suda et al., 2008). Experiments that mimic these fluctuations in hormones between gestation and the postpartum period have resulted in a depressive-like phenotype in rats (Galea et al., 2001; Suda et al., 2008). That said, the exact causes of peripartum mood and anxiety disorders in women are still not well-understood. We hypothesize that the unique changes in immune function that occur throughout pregnancy may also contribute to an increased risk of mental health disorders in the mother.

2.1. 1a. Immune dysregulation is associated with the risk of mental health disorders. Is this also true in pregnant and postpartum women?

Various studies over the past few decades have clearly demonstrated that elevated cytokine production promotes the expression of "sickness behavior", a highly organized behavioral effect of the immune system that allows an organism to fight infection as efficiently as possible through the induction of various behaviors including listlessness, decreased appetite, sleepiness, reclusion, anhedonia, and malaise (Dantzer, 2006, Dantzer, 2001, Dantzer et al., 2011, Dantzer et al., 2008). Many researchers have noted the similarity of these sickness behaviors with the symptoms seen in major depression, and as a result it has been suggested that significant increases in circulating cytokines may be linked to the development of mood disorders, most notably major depressive disorder (Alesci et al., 2005; Brambilla and Maggioni, 1998; Capuron et al., 2004). In patients with major depressive disorders, the production of specific cytokines (e.g. interferon, IL-6 and monocyte chemotactic protein 1, tumor necrosis factor, and macrophage inflammatory protein – 1a) can be exaggerated, correlating with an additional mental health pathologies, such as anxiety, in these individuals (Gaspersz et al., 2017). Moreover, immune molecules typically produced during infections, can induce major depression and even various forms of psychosis when injected directly into people or rodents (Miller et al., 2009). This evidence is particularly important given that pregnancy and the postpartum period are associated with an increased risk of mood disorders, but also other pathologies including anxiety and psychosis (Goodman et al., 2016; M'baïlara et al., 2005; Pawluski et al., 2017; Seyfried and Marcus, 2003).

A few studies indicate that perinatal depression is associated with alterations in cytokine production in the periphery, which would suggest that women diagnosed with perinatal depression are experiencing dysregulation of the immune system to some degree (Leff-Gelman et al., 2016; Osborne and Monk, 2013). Alternatively, the naturally occurring changes in cytokine production that result from pregnancy and pregnancy hormones may induce subsequent vulnerability to mood and anxiety disorders during pregnancy or the postpartum period. For example, a recent study found that circulating levels of IL-6, IL-15, and CCL3 were significantly *higher* at a third trimester visit in depressed pregnant women (Osborne et al., 2019a, 2019b). Given the limited and very preliminary studies such as these, an important area of focus for future research would be to systematically collect serum samples from a large cohort of women throughout gestation and the postpartum period in order to understand how and whether changes in circulating cytokine levels or associated pregnancy hormones can *predict* the onset of postpartum mood and anxiety disorders in these women. With diagnostic information such as this, basic biomedical researchers can in turn focus subsequent experiments on these pre-determined risk factors and how they induce specific neural changes and associated behavioral symptoms that are more likely to be precipitated throughout pregnancy and the postpartum period.

2.2. 1b. Are there changes in the brain's immune system during pregnancy that might contribute to the risk of peripartum mental health disorders?

To date, only a few studies, including our own, have examined the impact of pregnancy and parturition on cytokine expression in the periphery *and* the brain using rodent models. We have found that pregnancy significantly attenuates cytokine production in the periphery [Fig. 1A] *and in the brain* [Fig. 1B] following an immune challenge such as lipopolysaccharide (LPS). In the pregnant brain, these effects were robust – particularly within the hippocampus and prefrontal cortex, which are two brain regions associated with the etiology of depression (Sherer et al., 2017). In addition, we and others have found that female rats have elevated levels of IL-6, IL-4, and IL-10 within the hippocampus and prefrontal cortex immediately after birth, *even in the absence of an overt infection or immune challenge* (Haim et al., 2017; Posillico and Schwarz, 2016). Interestingly, these data are consistent with the idea that immune cells in the brain, microglia, shift their function towards the greater production of Th2-type cytokines, just as the peripheral immune cells do throughout pregnancy. These cytokines, in particular, can have a robust effect on programming immune cells,

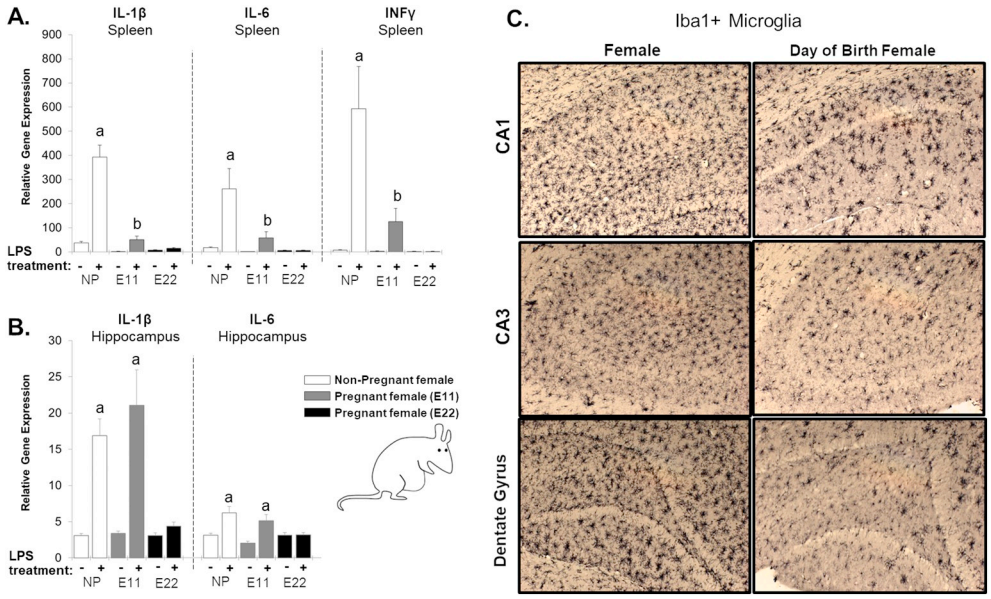

Fig. 1. Pregnancy significantly attenuates the peripheral and central immune response.
Non-Pregnant (NP) and pregnant female rats [embryonic day (E) 11 or E22)] were treated with 100 μg/kg of lipopolysaccharide (LPS, a bacterial cell wall component). The spleen (A) and hippocampus (B) were collected 4 h later and the expression of IL-1β, IL-6 and Interferon (IFN) γ were examined using qRT-PCR. We found a significant interaction of pregnancy and immune activation. Specifically, LPS elicits a strong cytokine response in the spleen and hippocampus of non-pregnant females (a = $p < 0.001$ relative to saline treated controls); however, this immune response is significantly attenuated throughout pregnancy in a tissue specific manner. At E11 cytokine expression is attenuated in the spleen (b = $p < 0.01$ compared to NP-LPS), but not the hippocampus. At E22, and cytokines are completely suppressed relative to untreated pregnant rats. (C) Iba1 staining of microglia reveals significant changes in cell density within the hippocampus (CA1, CA3 and dentate gyrus) immediately postpartum. Data adapted from Sherer et al. (2017); *Brain, Behavior and Immunity*.

including microglia in the brain, in response to subsequent activation (Lively and Schlichter, 2018; Siddiqui et al., 2016), and microglial function even in the *absence* of subsequent challenges (Lam et al., 2017). When we examined the density of microglia in these brain regions, we were surprised to find that there was a striking *decrease* in the density of microglia in the CA1 and dentate gyrus of the hippocampus on the day of birth, while in contrast, microglia were increased in their density within the CA3 of the hippocampus (Fig. 1C; (Posillico and Schwarz, 2016)).

A similar study by Haim and colleagues (2017) found that both microglial density and cell count were significantly reduced during late gestation and the early-mid postpartum period in additional brain regions including: basolateral amygdala (BLA) and the nucleus accumbens (NAc). They also determined that this reduction in microglial density occurred primarily in microglia with a thin, ramified morphology, which suggests that certain functions or specific microglial subtypes are affected by pregnancy, pregnancy hormones or parturition (Haim et al., 2017). These changes in microglia in the postpartum brain could be driven by microglial migration to other brain regions that are also undergoing changes at this time; however, they may also be attributed to reduced microglial proliferation as suggested in (Haim et al., 2017); however, the exact cause(s) of or reasons for these changes are currently unknown. Taken together, these findings suggest that changes in *neuro*immune function during pregnancy and the postpartum period are robust and widespread, impacting brain regions involved in learning, motivation, and mood; but also implicated in mood and anxiety disorders (Pawluski et al., 2017; Posillico and Schwarz, 2016; Post and Leuner, 2019; Sherer et al., 2018; Sherer et al., 2017). Moreover, female rats have shown postpartum anhedonia (Fig. 2), similar to a mild form of postpartum anhedonia that is common in humans (e.g. "baby blues") (M'baïlara et al., 2005; Seyfried and Marcus, 2003); yet the mechanisms underlying this effect and possible causes by which it could be extended beyond the immediate postpartum period require further investigation. If changes in peripheral cytokine levels or hormones levels during pregnancy could serve as biomarkers for these specific changes in neuroimmune function that in turn correlate with or predict the onset of peripartum mood disorders in the mother (Bränn et al., 2018), it would be an important and simple first step towards

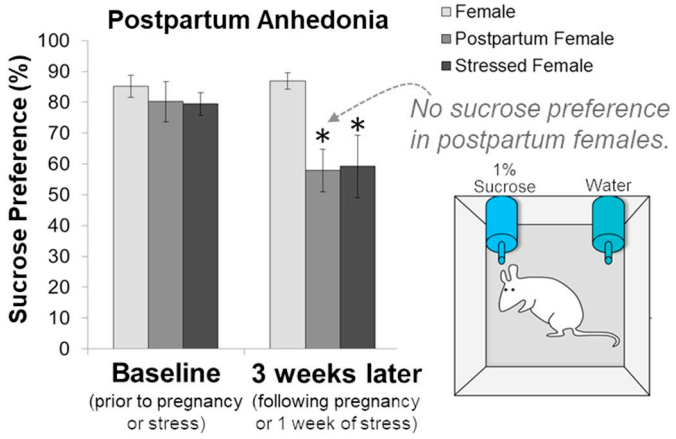

Fig. 2. Postpartum anhedonia in female rats.
Postpartum females (P1) also exhibit significant anhedonia, similar to that produced by 1 week of forced swim stress in non-pregnant females. * $p < 0.05$ RM-ANOVA w/ posthoc tests. Data adapted from Posillico and Schwarz (2016); Behavioral Brain Research.

understanding the etiology of mental health in women during the peripartum period.

Importantly, it should be noted that these changes in immune function during pregnancy are not limited to women with preexisting health conditions; rather, these changes in immune function are more *easily identifiable* in immunocompromised women. For example, women with autoimmune disorders usually find significant relief from the symptoms of their autoimmune disorders throughout pregnancy, an effect that reverses in the weeks after birth (Carp et al., 2012; Marder et al., 2016; Osborne et al., 2018a, 2018b). An important point, researchers have yet to determine the full impact of immune modulation during pregnancy on maternal health and well-being in other "at-risk" women, pregnant women who may be predisposed to low-grade inflammation or immune activation due to other factors including stress, hormones, mild infections, genetics or certain drugs that may further "prime" or alter the function of the immune system and its subsequent

modulation during pregnancy and the postpartum period. For example, one study found that prenatal stress in an inner-city cohort of pregnant women was associated with changes in immune responses in cord blood at the time of birth (Wright et al., 2010). These data suggest that environmental factors, such as stress (and associated elevated levels of stress hormones), can subsequently modulate immune function at the maternal-fetal interface – a finding that is mirrored by data from rodents (Bolton et al., 2017; Bolton et al., 2013). Moreover, numerous studies have demonstrated that even acute stress, let alone chronic exposure to environmental stressors, can result in widespread changes in cytokine production within the brain and periphery (Blandino et al., 2009; Bollinger et al., 2017; Winkler et al., 2017). As a result, we hypothesize that women with low-grade inflammation or subtly altered immune function caused by stress or other environmental factors may be at a greater risk for mental health-related pathology during pregnancy and the postpartum period, however, this remains to be determined.

Finally, peripartum mood disorders may impact the quality of maternal care and mother-infant interactions (recently reviewed by (Brummelte and Galea, 2016; Fig. 4). For example, postpartum depression can be associated with a decrease in mother-infant interactions postpartum (Beck, 1995; Feldman et al., 2009; Lovejoy et al., 2000). In rodent models, stress or treatment of dams with corticosterone during pregnancy can prevent the appropriate induction of maternal behaviors and the associated changes in the maternal brain (Brummelte and Galea, 2010; Hillerer et al., 2012; Tronick and Reck, 2009). There is ever-growing support amongst researchers and clinicians that deficits in parental care can increase the risk of later-life behavioral disorders, stress dysregulation and adult pathologies in the offspring (Loman et al., 2010; Walker et al., 2017). Thus not surprisingly, postpartum depression can be associated with negative mental health outcomes in children (Tronick and Reck, 2009). Children of mothers suffering from postpartum depression are at risk for emotional, behavioral and psychological problems, as well as, cognitive delays (Grigoriadis et al., 2013; Murray et al., 2010; Scott et al., 2016; Suri et al., 2017). Poor or inconsistent maternal care, even in rodent models, can also result in long-term changes in brain development and the expression of neurotrophic factors in the offspring, thereby increasing the risk of poor mental health outcomes (Roth and Sweatt, 2011). Thus as we continue to gain a better understanding of the interactions between the immune and endocrine systems that occur throughout pregnancy, and how they can be altered or exacerbated by environmental factors or stress, we have the potential to hopefully prevent the onset of mental health disorders in the mother, thereby increasing the quality of life for both her and her infant.

3. Part 2. A neurodevelopmental perspective of mental health disorders associated with immune dysregulation during gestation and beyond

While pregnancy is associated with dramatic immunosuppression in the mother, the immune system of her developing fetus is also relatively underdeveloped (Jenmalm, 2017; Marshall-Clarke et al., 2000; Ortega et al., 2011). Birth represents a transition from intrauterine “sterility” (although some argue that the in utero environment is not completely “sterile”; Perez-Muñoz et al., 2017) to *ex utero* self-sufficiency against a world of pathogens and physiological stressors. Yet the evidence suggests that the immune system of the newborn isn't yet equipped to handle pathogens. It is clear that the perinatal immune system is not deficient; however, it is underdeveloped and ultimately contributes to an increased risk of infection both in utero and neonatally (Collins et al., 2018; Levy, 2007; Levy and Wynn, 2014; Osrin et al., 2004; Ygberg and Nilsson, 2012). One in 10 newborns will be born prior to 36 weeks of gestation (preterm); and infection and sepsis in preterm and neonatal infants remain a significant clinical problem that represents a substantial burden to the healthcare system (Collins et al., 2018). Similarly, viral infections, such as maternal influenza infection, results in increased cytokine production via the activation of the maternal immune system, the fetal immune system, and even immune cells within the placenta (Ashdown et al., 2006; Careaga et al., 2017; Garay et al., 2013; Kentner et al., 2019; Smith et al., 2007; Urakubo et al., 2001). Limited *adaptive* immunity in the mother (during pregnancy) and the newborn places a greater burden on the innate immune system to respond in the presence of an immune challenge, a phenomenon that continues into the first years of a newborn's life (Levy and Wynn, 2014). However, innate immune function is also underdeveloped in neonates, as it produces a different set of cytokines in response to infections relative to these same infections in healthy adults (Belderbos et al., 2009; Burl et al., 2011; Hebra et al., 2001; Kollmann et al., 2009; Levy, 2007; Levy, 2005). Similarly, in rodents, the expression of cytokines in the periphery *and brain* following activation of the innate pattern recognition receptor, Toll-like receptor 4 (TLR4), is *severely* blunted just one day after birth compared to the juvenile or adult immune response (Ortega et al., 2011). Importantly, very little is known about the interactions of the developing immune and nervous systems; thus we know very little about how perturbations or activation of the immune system early in life, may impact the on-going development of neural circuits underlying specific behaviors.

Evidence from the human literature implicates the activation of the immune system during development in a number of neuropsychiatric and neurodevelopmental disorders. These neurodevelopmental disorders include schizophrenia, autism, anxiety disorder, major depressive disorder, generalized pervasive developmental disorders, as well as cognitive or learning deficits. In particular, there is an emerging literature to suggest that immune dysregulation early in life may lead to cognitive and behavioral disorders that persist throughout the lifespan (Frick et al., 2013; Leckman, 2014; Maezawa et al., 2011; O'Connor et al., 2014; Tay et al., 2017a). We propose that similar causal mechanisms, such as immune activation or dysregulation early in life, and associated changes in cytokine expression, may play a role in and lead to markedly varying degrees of mental health and cognitive disorders, from simple learning disorders to severe forms of autism or schizophrenia, depending on the age of and severity at onset.

3.1. 2a. How does immune dysregulation during brain development result in the onset of cognitive or mental health disorder?

Our lab has been investigating how the activation or dysregulation of the immune system can disrupt the ontogeny of neural circuits and their associated behavior. To that end, we have been examining how the timing of early-life immune activation can disrupt the development of hippocampal dependent learning. For example, we recently found that activation of the developing immune system on postnatal day (P) 21 produces a robust deficit in the onset of hippocampal-dependent learning on P24 (Fig. 3A). Our working hypothesis is that immune activation on P21 was sufficient to disrupt the proper development of hippocampal circuits necessary for this type of learning. In support of this working hypothesis, we have also found that treatment of rats just three days later at P24 with LPS (100 μg/kg) ***does not*** result in a learning deficit when tested three days later (P27, Fig. 3B), likely because these neural circuits responsible for learning were established *prior* to P24, prior to the immune activation. Next, we examined the cytokine response and the associated changes in microglial-neuronal communication molecules and synaptic plasticity molecules that were induced by the LPS challenge at P21. We found that the peak of the cytokine production (e.g. IL-1β and IL-6) occurred between 4 and 8 h post LPS administration, and was resolved within 24 h post LPS administration. LPS induced a change in the expression of microglial-neuronal communication molecules, including fractalkine and complement (C)3, as well as Brain Derived Neurotrophic Factor that emerged later, and persisted at 24 h post immune activation. Thus, we conclude that the observed learning deficits at P24 are not the *direct*

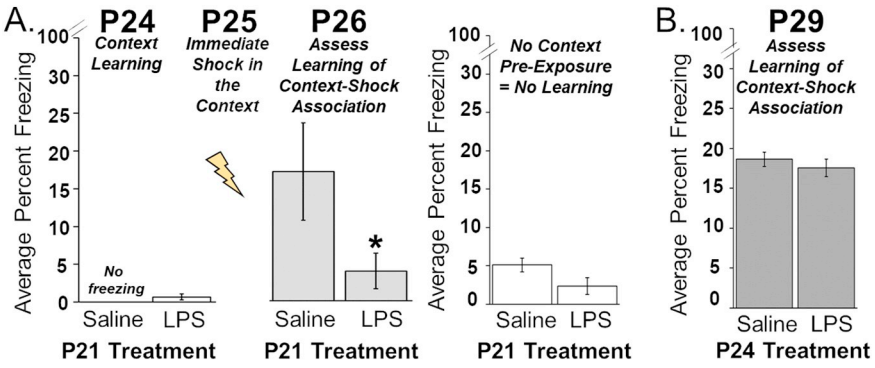

Fig. 3. Assessing immune-precipitated cognitive deficits using Context Pre-exposure Facilitation Effect (CPFE) paradigm. (A) On Day 1 of the CPFE (P24), rats explore the context for 5 min and all rats show no, or almost no, freezing. On Day 3 (P26), only rats that received LPS treatment (100 μg/ml/kg) on P21 show significantly less freezing compared to saline treated rats (*$p < 0.05$) during the 5 min test, regardless of previous neonatal immune activation. In concurrent behavioral controls, rats show the "immediate shock deficit" (ISD) during the 5 min test on Day 3 after receiving only the immediate shock on Day 2, with no context pre-exposure, indicating that the learning on P24 is context-hippocampal-dependent. (B) Rats treated with LPS on P24 (after the full emergence of learning) show no learning deficits when tested days later (P29). Brittany F. Osborne's unpublished data.

result of cytokine production itself, as this was resolved days earlier (unpublished data). Rather these learning deficits likely emerged as a result of changes in the neural circuits underlying this type of learning that were initiated following the original cytokine response. Ongoing experiments in our lab are currently examining how immune dysregulation at P21 affects hippocampal circuit formation during this unique period of neural development. We are also examining whether these deficits in learning caused by immune activation are persistent. The question remains how aberrant behavior can persist long after the initial immune challenge has resolved itself, such as that seen in our current model and in many neurodevelopmental disorders (Scott et al., 2016). Understanding how aberrant behavior persists following immune activation or dysregulation is essential to understanding the link between early-life immune activation and the subsequent etiology of many neurodevelopmental and mental health disorders. If, in our model, learning deficits do not persist into later ages, it would be interesting to know how microglia can remodel neural circuits outside the original timeframe during which these important neurodevelopmental events typically occur. Understanding how microglia can remodel neural circuits outside of a specified neurodevelopmental window would be transformative, as it would allow us to better understand whether and how dysfunctional neural circuits might be rewired later in life by targeting the function of these immune cells.

3.2. 2b. Sex differences in neuroimmune function: Another layer of interaction that likely impacts lifelong mental health outcomes

Sex is an important biological variable that significantly impacts a number of physiological systems, including the immune, endocrine and nervous systems. In mammals, an individual's sex is determined as male or female by the presence of the sex chromosomes, the differentiation of the reproductive organs, and the subsequent production of sex-specific hormonal patterns that in turn organize the brain as male or female. Every cell has a sex; thus, biological sex differences can influence the immune response that in turn impacts recognition, clearance, and transmission of pathogens, as well as their subsequent impact on neural development and behavior. For recent reviews on the topic see (Klein and Schwarz, 2018; Nelson et al., 2018; Tay et al., 2017b; VanRyzin et al., 2018; Villa et al., 2018a).

Many sex differences in the brain are established during a critical period of brain development (McCarthy et al., 2017); and numerous studies elegantly demonstrate the important role of sex hormones in organizing the brain and behavior as either male or female prenatal development in humans and other primates and in postnatal development of altricial species such as rodents. More recently, two lines of research have provided significant insight into the mechanisms responsible for sexual differentiation of neural circuits during the critical period of development, and the potential impact that this process may have *following* an early-life immune challenge. First, studies by Lenz et al. (2013) demonstrated that the resident immune cells of the brain, microglia, are a fundamental mechanism by which the development of sexually dimorphic neural circuits in the preoptic area (POA) establish *sex-specific behaviors*. During the critical period of sexual differentiation, microglia within the POA release the immune signal, prostaglandin E_2 (PGE_2), which masculinizes neural circuits in the developing male POA via crosstalk between surrounding astrocytes and neurons (Lenz et al., 2013; Lenz et al., 2011; McCarthy et al., 2008; Wright and McCarthy, 2009). Furthermore, females treated with either testosterone, converted to estradiol in the brain, or PGE_2 alone can masculinize the number and morphology of microglia in the female brain, such that inhibition of microglial function prevents adult male sex behavior later in life (Lenz et al., 2013). These findings were the first to directly link sex differences in microglia number and morphology with the development of the sexually dimorphic neural circuits that control reproductive behaviors.

The second line of research has investigated how sex differences in microglia number and morphology influence the development of neural circuits in regions that do not yet have a clear role in sexually dimorphic behaviors. Studies from our lab and others have shown that neonatal male rats have significantly more microglia than females in the parietal cortex, CA1, CA3, dentate gyrus (DG), and amygdala (Nelson et al., 2017; Schwarz et al., 2012); and, compared to females, a larger percentage of microglia in male brain have an amoeboid morphology, indicating a more immature "phenotype" (Schwarz et al., 2012). These sex differences in microglia number and morphology are evident on postnatal day 4 (P4) and are the result of increased testosterone-mediated cell proliferation in the male brain, and *not* the result of decreased cell survival in the female brain (Nelson et al., 2017). Moreover, these sex differences shift throughout development, as others have recently reported various sex differences in microglia number or function at various ages, including P8 and P28 (Hanamsagar et al., 2017; McCarthy, 2019; Nelson et al., 2018; Villa et al., 2018b; Weinhard et al., 2018). In fact, neonatal female rats treated with estradiol (derived from testosterone) have increased microglia cell proliferation, similar to that seen in males (Nelson et al., 2017), indicating that microglia can respond to sex steroid hormones to influence their number and perhaps function (Baker et al., 2004; Loram et al., 2012). But, it is not *exactly* clear how this occurs. Several groups have demonstrated that expression of steroid hormone receptors is either extremely low or undetectable in microglia during early brain development (Crain et al., 2013; Lenz et al., 2013; Turano et al., 2017). Moreover, systematic analysis of microglial activation at various ages suggests that the microglial *response* to an immune challenge may not be wildly different between males and females (Lively et al., 2018; Osborne et al., 2019a, 2019b; Turano et al., 2017). Taken together these data suggest that cross-talk between microglia and other neural cells that *do* robustly express steroid hormone receptors, or cross-talk between microglia and the peripheral immune system may be necessary to produce sex differences in microglia number and effects in the

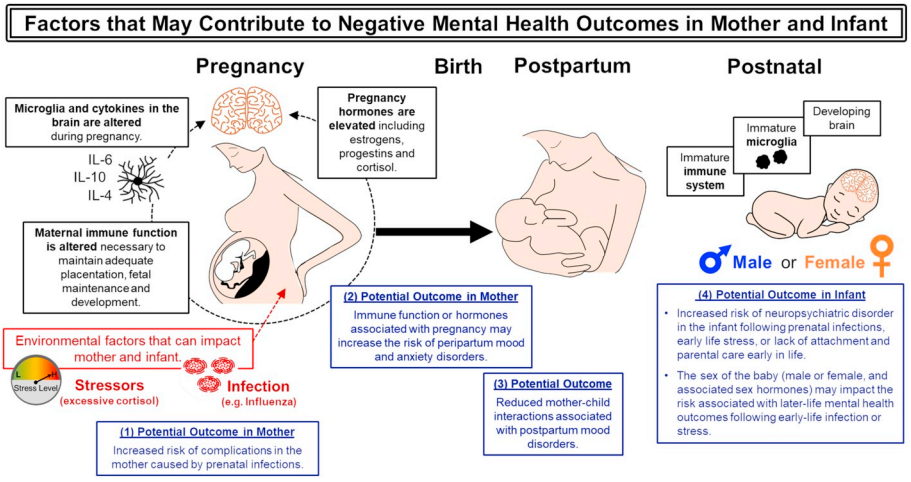

Fig. 4. Factors that may contribute to negative mental health outcomes in mother and infant. During pregnancy, hormones are elevated and maternal immune function is significantly altered. Both are physiological changes necessary to maintain a successful and healthy pregnancy. In addition, microglia number and cytokine production are altered in the maternal brain during pregnancy and the immediate postpartum period. As a result, mothers are (1) at increased risk for complications associated with prenatal infections or stress, and (2) at increased risk of peripartum mental health disorders. Changes in postpartum mood can result in (3) reduced mother-infant interactions, a significant risk factor for developmental disorders in the infant (Scott et al., 2016). Finally, (4) early-life stress or immune activation can result in increased risk of developmental or neuropsychiatric disorders in the infant, dependent upon the sex, age and severity at onset.

developing brain (Klein and Schwarz, 2018; Turano et al., 2017). Importantly, evidence suggests that depleting microglia during the immediate postnatal period differentially effects a number of behaviors, including mood and social behaviors, differently in males and females (Nelson and Lenz, 2017). Thus, the question remains whether *activation* of microglia, though the initial immune response may be quite similar in males and females, disrupts important on-going processes of neural development differently in males and females (McCarthy, 2019; Schwarz and Bilbo, 2012).

Important to this discussion, is emerging evidence that males are more vulnerable than females to a number of neurodevelopmental disorders that also have their origins associated with immune activation or stress during development (Bao and Swaab, 2010; Bilbo et al., 2018; Hanamsagar and Bilbo, 2016; McCarthy, 2019; Osborne et al., 2018a, 2018b; Schwarz and Bilbo, 2012). Thus as we consider the interaction of the maternal-fetal immune systems or the neonatal immune systems with the endocrine and neural systems, we must also consider the potential role of sex in these interactions and the outcomes associated with early-life or maternal immune activation (see Fig. 4 for a summary).

4. Conclusions

It is important physicians and scientists recognize that pregnancy and the postpartum period are periods of significant change in the immune and endocrine systems. This period of life is associated with an increased risk of mental health disorders in the mother, as well as her offspring. As a final take-away point, the collective data supports the idea that developmental disorders and depression likely reflects multiple etiologies leading to various symptom constellations, and thus these diagnostic terms may be too broad. In this case, testing the mechanisms underlying *specific symptoms* (such as deficits in specific types of learning or the onset of anhedonia, as we have done in our own lab) may provide a unique understanding of the constellation or multiple etiologies that most likely underlie the various types of mental health disorders in humans. The results of future experiments should attempt to advance our understanding of how the interactions between these various peripheral and central factors contribute to maternal mental health, while simultaneously understanding the impact it has on the developing brain of the offspring. These research questions may not be easy to tackle given the various factors to consider and control for, but the answers to these questions will be informative and make us better equipped to improve the long-term quality of life for both mother and infant.

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