# Prenatal Stress and the Microbiome: Relevance to Neurodevelopment

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Mental illnesses are highly heritable, and while transmission is partially genetic, genetics do not underlie the entire contribution. Maternal stress and illness during pregnancy also exert influence on the developing infant and factor into the mechanisms underlying psychopathology. Indeed, infants exposed to antenatal stress and maternal anxiety demonstrate increased risk of developing altered stress response, anxiety disorders and depression in adulthood.[1] Mechanistic understanding of how stress alters the intrauterine environment and affects the developing nervous system is lacking.

Adverse prenatal events, including maternal stress, have the capability of negatively influencing the neurodevelopment of the fetus, with long term cognitive and behavioral implications.[2] The interplay between intrauterine growth factors, hormones, and the immune system is dynamic and integral to healthy development in the fetus. Recent studies have reported that the placenta harbors a unique microbial population,[3] though this remains a controversial and open question. Microbes are an essential part of the gut-brain axis, which has been gaining momentum and evidence over the past several years as being an important contributor to mental health. Stress is known to lead to gut microbiota dysbiosis, though whether this plays a role in transmission of stress from mother to offspring is largely unknown.

Therefore, we decided to test the hypothesis that prenatal stress alters the maternal microbiome, leading to dysbiosis, inflammation, and changes in growth factors *in utero* and into adulthood. In order to test this, fecal and placental samples were collected from mouse dams and adult offspring. Microbial diversity was assessed using the Illumina MiSeq® platform, for targeted 16S ribosomal RNA gene sequencing. We now have evidence that prenatal stress alters maternal microbiota, placental microbes and leads to dysbiosis in adult female[4] and male offspring. Furthermore, in placentas of female origin we report significant increases in cytokines and chemokines, as well as a significant decrease in brain derived neurotrophic factor (BDNF). BDNF is a critically important trophic factor involved in synapse formation and neurodevelopment. We also found a significant decrease in BDNF, and an increase in cytokines, in the adult female hippocampus, a brain region important in memory and mood regulation. We therefore performed several experimental behavioral paradigms in the female offspring, to see whether the dysbiosis, inflammation, and change in BDNF were associated with aberrant behavior. Indeed, we found a concomitant increase in anxiety-like behavior and decrease in cognitive ability in females exposed to prenatal stress. Together, these data suggest that prenatal exposure to stress leads to alterations in microbiome, cytokines and BDNF *in utero*, and this continues into adulthood, and is accompanied by increased anxiety-like behavior and changes in cognition in female offspring (Fig 1).

In regards to males, while they had dysbiosis in adulthood, the subsequent biological consequences differed from those found in females. In male-derived placentas, we found a significant increase in corticotropin-releasing hormone (CRH), and a significant decrease in 11β-hydroxysteroid dehydrogenase



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type 2 (11β-HSD2), which breaks down the stress hormone corticosterone. Thus, the male fetuses appear to be exposed to altered corticosterone, an important stress hormone, *in utero*. They also demonstrate a significant alteration in their hypothalamic-pituitary-adrenal axis (HPA Axis) into adulthood, along with decreases in oxytocin receptor levels. Associations with alterations in the HPA Axis and autism have been described in the human literature in regards to individuals with autism spectrum disorder (ASD).[5,6] In addition, we found a significant reduction in monoamine oxidase A (MAO-A), an enzyme responsible for breaking down monoamines like serotonin, in male-derived placentas. This suggests that male fetuses were developing in a milieu with altered levels of monoamines, which could directly impact neurodevelopment. The decrease in MAO-A continued into adulthood. Adult male brains also demonstrate increased levels of cytokines IL-6 and IL-1β (interleukin). Both alterations in MAO-A[7] and neuroinflammation[8,9] have been tied to social behavior. We therefore examined behavior in a social approach paradigm, which measures the preference of a test mouse to a stimulus mouse, in comparison to an object. Male offspring exposed to prenatal stress showed a significant reduction in social behaviors when compared to controls (manuscript in preparation). Together, these data suggest that exposure of the male fetus to prenatal stress alters exposure to corticosterone *in utero* and continued alterations in the HPA Axis, oxytocin, microbiome, neuroinflammation and social behaviors in adulthood (Fig 1).

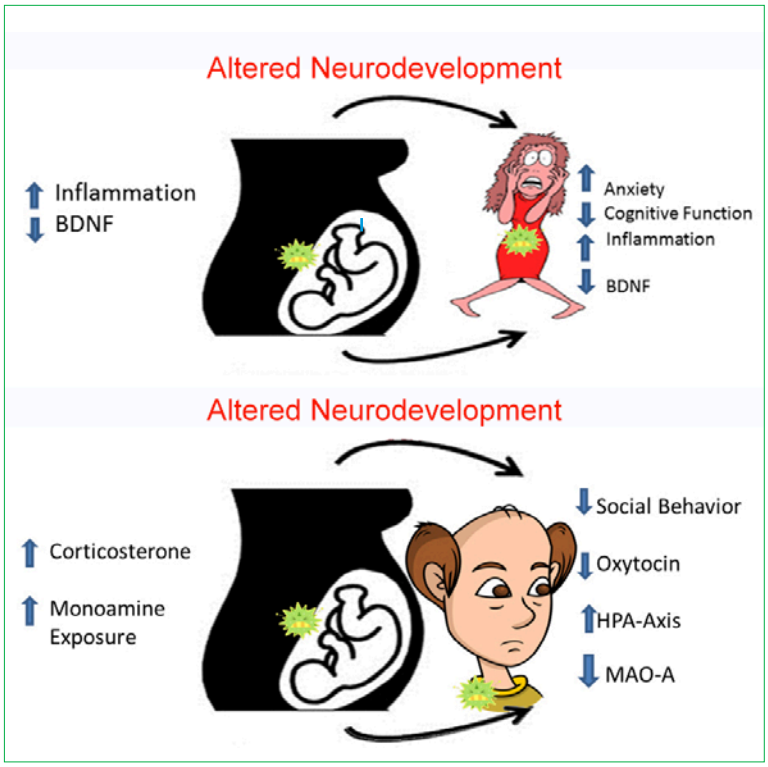


**Fig 1. Impact of prenatal stress on neurodevelopment.**

BDNF= brain derived neurotrophic factor, HPA-Axis=hypothalamic-pituitary-adrenal axis, MAO-A= monoamine oxidase A

It has been well established that there are pronounced sex differences in the frequency and severity of psychiatric disorders, with depression and anxiety more prevalent in females, whereas psychosis, autism spectrum disorders and externalizing disorders more prevalent in males.[10-13] These studies begin to establish that some of these sex differences could originate from differential effects of the microbiome on male and female offspring as they are influenced by maternal stress. Pinpointing the contribution of the microbiome and subsequent immune response and trophic factor alterations to modifications in neurodevelopment in



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the offspring are an essential part of increasing the fund of knowledge regarding the impact of prenatal stress on neurodevelopment. Gaining a mechanistic understanding of how alterations in the placental microbes influence inflammation and neurodevelopment will support use of prebiotics or probiotics during pregnancy to improve mental health outcomes in offspring.

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