

# “Prenatal Stress, Glucocorticoids and the Programming of the Brain” (2001), by Leonie Welberg and Jonathan Seckl

In 2001, researchers Leonie Welberg and Jonathan Seckl published the literature review “Prenatal Stress, Glucocorticoids, and the Programming of the Brain,” in which they report on the effects of prenatal stress on the development of the fetal brain. The fetus experiences prenatal stress while in the womb, or in utero. In discussing the effects of prenatal stress, the authors describe prenatal programming, which is when early environmental experiences permanently alter biological structure and function throughout life. Throughout “Prenatal Stress, Glucocorticoids and the Programming of the Brain,” Welberg and Seckl provide a number of potential biological explanations, derived from both animal and human studies, to explain the underlying mechanisms involved in programming, which helped establish how in utero stress can affect fetal brain development.

In their article, Welberg and Seckl define perinatal programming as the process of non-genetic factors acting early in life to permanently affect the body. Perinatal means occurring in the time immediately before and after birth, while prenatal refers to the time during pregnancy. The authors write that the adaptability of a fetus may allow environmental factors during pregnancy to alter the development of the fetus in preparation for the environment after birth. However, if the environment is not similar to what the fetus experienced in the uterus, then negative health outcomes such as disease may result. For example, studies have shown that low birth weight predicts a significantly increased risk of hypertension, or high blood pressure, in adulthood. The researchers suggest that it is unlikely that low birth weight is the cause of increased likelihood of hypertension. Rather, Welberg and Seckl state that it is more likely that there is a common factor influencing low birth weight and the later development of hypertension, which they claim demonstrates a programming effect. In other words, the programming effect would be the stress that the fetus experienced in the uterus, which causes low birth weight, and the external environment that causes stress later leads to hypertension in the child after birth.

The authors’ research centers on how the fetus develops in a pregnant woman’s uterus and how outside factors can affect development. While the development of a fetus depends mostly on the uterus itself and the fetus’s ability to receive signals from its own developing cells, factors outside of the uterus can also play a role. For example, the authors’ research areas focus on the effects of biological signals, particularly stress signals, transferred from the pregnant woman to the fetus through their shared blood supply. If a pregnant woman is stressed because of variables in her environment, she secretes stress hormones, which can transfer to the fetus throughout pregnancy, during the birthing process, or directly after the birthing process, potentially impacting the development of the fetus. From an evolutionary perspective, if the pregnant woman is in a stressful environment, then those stress signals transmitted in utero may help the fetus better adapt to the stressful environment once it is born. However, if the environment outside the uterus is not one in which the infant is biologically stressed, then the eventual effects of the prenatal stress may be negative for the fetus, resulting in diseases or other negative health outcomes after birth.

“Prenatal Stress, Glucocorticoids and the Programming of the Brain” is a literature review on the effects of a stressful perinatal environment on the fetal brain. The authors, Welberg and Seckl, worked together at the University of Edinburgh in Edinburgh, Scotland. There, Welberg researched the role of stress in the development of depression in animals. She wrote numerous articles related to the effects of perinatal programming on health outcomes in addition to “Prenatal Stress, Glucocorti-

coids and the Programming of the Brain.” Seckl researched the genetic and molecular processes of the development of endocrine disorders, which are disorders dealing with hormone secretion in the body. He primarily focused on disorders of the brain. In their article, Welberg and Seckl state that existing studies supported the idea of programming. However, they also assert that, at the time of the article’s publication in 2001, scientists did not understand the underlying biological mechanisms of that effect. Throughout their article, the authors provide multiple potential explanations for the underlying mechanisms involved in filling that gap in the scientific literature. Welberg and Seckl also focus on the involvement of the central nervous system in the process of programming, claiming the majority of studies at the time largely focused on the metabolic and cardiovascular systems instead.

In their article, the authors discuss five main concepts, broadly separated into sections. First, they explain that prenatal stress negatively affects a number of factors in the fetus, such as anxiety levels and cognitive abilities. Welberg and Seckl suggest that those negative effects may be caused by alterations in the fetus’s brain development during pregnancy due to exposure to prenatal stress. In the next sections, the authors describe how maternal stress hormones during pregnancy may affect the development of the fetus’s brain in the uterus, leading to improper regulation of stress and the development of disorders later in life. Then, the authors discuss how the fetus may have forms of protection against maternal stress hormones, reducing the effects of programming. Next, Welberg and Seckl offer some possible explanations for the mechanisms underlying the programming effects and note that future researchers could investigate other factors, such as genetics and the environment after birth. In the final section, the authors discuss how applying the findings of the animal-based studies discussed in the article may point to a possible connection between prenatal stress and the development of disorders in adult humans.

In their article’s first section, Welberg and Seckl review existing claims that prenatal stress programs brain function while describing potential underlying mechanisms causing that programming. The authors write that the brain is susceptible to programming because of its long and complex development process. In their review, the researchers write that one of the most studied components of the nervous system which is prone to programming’s effects is the hypothalamic-pituitary-adrenal, or HPA-axis. The HPA-axis is the body’s central stress response system regulating the release of glucocorticoids, among other hormones. It involves the hypothalamus, the pituitary gland, and the adrenocortical system, all of which engage in regulating the body’s numerous systems with hormones. Glucocorticoids, a type of stress hormone, affect nearly every organ and tissue in the body and regulate numerous biological processes including immune function, growth, reproduction, cognition, and behavior. One of the main glucocorticoids involved in stress regulation is cortisol, which is released by the adrenal glands and is also responsible for regulating metabolism, blood pressure, and helping memory formation. Prenatal stress can permanently increase the release of hormones eliciting the body’s response to stress for the developing fetus.

Since glucocorticoids interact with other hormones and parts of the body to regulate behavior and HPA activity, the authors suggest that it is possible that permanent alterations of systems involved in the HPA-axis can cause lasting effects after birth, such as anxiety. In explaining their reasoning, Welberg and Seckl state that prenatal stress has long-standing programmed effects on the HPA-axis, usually resulting in anxiety for the individual after birth. They explain that, in other studies, prenatal stress caused reduced movement in rats and reduced inclination to play, among other observed factors. Similarly, prenatal stress can affect an adult’s cognition because prenatal exposure to high levels of cortisol can cause damage to the developing brain. For example, studies have indicated a different, more rigid strategy-forming process in prenatally stressed animals, as well as worse working memory in old age. The authors suggest that those cognitive effects may be the result of damage caused to the developing brain prenatally, because high prenatal cortisol damages some parts of the brain responsible for cognitive tasks. However, Welberg and Seckl acknowledge that the underlying mechanisms are not well-established, which the authors discuss in the next section.

Next, the authors describe hypotheses of potential programming factors and their underlying mechanisms. Since cortisol is an important part of stress response, one major hypothesis is that cortisol is the primary programming factor. In other words, if a pregnant woman secretes a lot of cortisol, that cortisol transfers into the fetus’s body through their shared blood supply, which may cause

the fetus's brain to develop differently. Welberg and Seckl state that studies show that prenatal stress is correlated with later development of hyperglycemia and hypertension, which are disorders characterized by elevated amounts of glucose in the bloodstream and abnormally high blood pressure, respectively. Other researchers have also linked the two disorders with low birth weight and prenatal stress. Thus, the authors claim that it is possible that prenatal stress may be the link between those disorders and low birth weight.

Then, Welberg and Seckl report that studies have shown that rats that were stressed prenatally can have altered adult behavior and brain development, suggesting that prenatal stress may have caused those effects by affecting the brain through programming. They explain that the behavior changes may be the result of altered functioning of the amygdala, which is the part of the brain regulating fear and anxiety. The authors suggest that prenatally stressed animals may have increased stress levels in adulthood because of an increased signal for stress hormones in the amygdala that gets influenced while they were fetuses. In other words, the animals have a biological overreaction to stress that seems to have been conditioned very early in life through a kind of programming. Additionally, Welberg and Seckl discuss the possibility that there is a specific time frame in which prenatal programming occurs, since effects were only observed in studies when rats were exposed to specific amounts of stress during specific times throughout pregnancy. The researchers describe that the time frame may also be an important factor to consider in determining how the programming occurs.

In their article's next section, Welberg and Seckl explain that fetuses have a biological protection from maternal stress hormones, which may mitigate the effects of programming. Some researchers believe that a certain fetal gene, known as placental 11-beta hydroxysteroid dehydrogenase, protects the fetus from maternal stress hormones. When certain factors inhibit the gene, more maternal stress hormones reach the fetus and alter fetal growth and tissue development, and also affect programming as a result. For example, the authors provide a study in which the gene was inhibited in rats yielded lower birth weights and programming for hypertension and hyperglycemia later in life. Thus, that gene may also be important to consider in understanding the effects of prenatal stress. The authors then note that maternal malnutrition may also be a significant factor since it reduces the fetus's production of that gene, which would allow for greater exposure to prenatal stress.

In the following sections, Welberg and Seckl offer a number of possible explanations for the mechanisms underlying the programming effects of prenatal stress. The first explanation is that prenatal stress hormones affect the transcription of the fetuses' stress hormone receptors directly, permanently altering the receptors' abilities to regulate stress. In other words, the fetus's genetics are altered directly, leading to a worse ability to regulate stress. Another possibility the authors describe is that maternal stress hormones permanently affect the fetuses' developing neurotransmitter systems, which affect the functioning of the hormone receptors as a result. Neurotransmitter systems enable the body's nerve cells to communicate with one another. Hormone receptors receive messages from substances in the bloodstream to direct the activity of cells. If neurotransmitter systems cannot enable nerve cells to communicate properly, then hormone receptors cannot direct the body's reaction to stress correctly, causing health issues for the child. The researchers also suggest that prenatal stress affects the regulation of growth hormones, which in turn affects development, possibly causing diseases later in life. However, the authors note that future researchers should consider factors other than the underlying processes, such as genetics and the postnatal environment. Researchers should consider those additional factors since the factors can mitigate or worsen the effects of programming.

Lastly, the authors discuss how similar findings in humans may provide further understanding of the effect of prenatal programming. While most of the studies discussed in their article are animal-based, the authors note that similar associations between low birth weight and later development of disorders occur in humans. The researchers also state that people should be cautious when applying the results to humans, since there is evidence that prenatal malnutrition, rather than glucocorticoid variations, of human fetuses may be involved in the development of specific issues in adulthood, such as obesity and even schizophrenia. Additionally, several researchers have associated prenatal stress with premature birth, low birth weight, and the later development of psychological issues

for the fetus. Researchers have also correlated low birth weight with increased cortisol levels. The authors conclude that the findings point to a possible connection between prenatal stress and the development of stress-related and behavioral disorders later in life. Additionally, they write that it is possible that negative health outcomes caused by prenatal and perinatal programming could be beneficially modified in the postnatal environment to reduce or reverse effects. Welberg and Seckl emphasize that further research is needed.

Other researchers have cited "Prenatal Stress, Glucocorticoids, and the Programming of the Brain" over 1000 times as of 2020, largely those also studying the effects of prenatal and perinatal programming. Additionally, researchers have used the article in studies outside the scope of programming specifically, including research on the relationship between stress and the development of eating disorders.

In "Prenatal Stress, Glucocorticoids and the Programming of the Brain," Welberg and Seckl provide a number of possible explanations for the underlying mechanisms of programming, filling a gap in the existing literature and providing recommendations for further investigation. By outlining the known effects of prenatal stress through their literature review, the authors provided evidence for the existence of programming effects. At the time of the article's publication in 2001, Welberg and Seckl advanced the understanding of prenatal and perinatal programming and provided a starting point for further investigation of the biological processes of programming.

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