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Review

Prenatal stress and genetic risk: How prenatal stress interacts with genetics to alter risk for psychiatric illness

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ABSTRACT

Risk for neuropsychiatric disorders is complex and includes an individual's internal genetic endowment and their environmental experiences and exposures. Embryonic development captures a particularly complex period, in which genetic and environmental factors can interact to contribute to risk. These environmental factors are incorporated differently into the embryonic brain than postnatal one. Here, we comprehensively review the human and animal model literature for studies that assess the interaction between genetic risks and one particular environmental exposure with strong and complex associations with neuropsychiatric outcomes—prenatal maternal stress. Gene-environment interaction has been demonstrated for stress occurring during childhood, adolescence, and adulthood. Additional work demonstrates that prenatal stress risk may be similarly complex. Animal model studies have begun to address some underlying mechanisms, including particular maternal or fetal genetic susceptibilities that interact with stress exposure and those that do not. More specifically, the genetic underpinnings of serotonin and dopamine signaling and stress physiology mechanisms have been shown to be particularly relevant to social, attentional, and internalizing behavioral changes, while other genetic factors have not, including some growth factor and hormone-related genes. Interactions have reflected both the diathesis-stress and differential susceptibility models. Maternal genetic factors have received less attention than those in offspring, but strongly modulate impacts of prenatal stress. Priorities for future research are investigating maternal response to distinct forms of stress and developing whole-genome methods to examine the contributions of genetic variants of both mothers and offspring, particularly including genes involved in neurodevelopment. This is a burgeoning field of research that will ultimately contribute not only to a broad understanding of psychiatric pathophysiology but also to efforts for personalized medicine.

1. Introduction

1.1. Prenatal stress as a risk for psychiatric illness

Prenatal maternal stress is a risk factor for multiple offspring neuropsychiatric disorders. While some specific physiological (e.g. immune activation, malnutrition, and low birth weight) and toxic stressors (e.g. alcohol and pesticides) are also of great importance as prenatal neuropsychiatric risk factors (Brown et al., 1996; Hellemans et al., 2010; Marques et al., 2015; Mathewson et al., 2017; Saeedi Saravi and Dehpour, 2016; Scola and Duong, 2017), psychological stress during the prenatal period is of particular interest for several reasons, detailed here.

First, *psychological stress can be induced in various ways*, e.g., in response to negative life events, such as disruption of social networks, or due to uncontrolled emotional psychiatric symptoms, among many others. Robert Sapolsky conceptualized stress as originating in the brain, when an individual perceives that he/she must respond to new demands (Sapolsky, 2015). This requires many different forms of allostasis, a term coined by another influential stress researcher, Bruce McEwen, to allow the entire physiology of an individual to meet these new requirements (McEwen, 2006).

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Second, Sapolsky and McEwen have both been fundamental in demonstrating that *psychological stress involves many changes across the entire physiology* of an individual (Lambert and Lambert, 2011; McEwen, 2006; Powell et al., 2013). Physiological changes during psychological stress include cardiovascular changes, immune system responses, stress hormone alterations, changes in neurosteroids, and sympathetic nervous system activation. This broad nature of these changes is particularly relevant to prenatal stress, where an *in utero* offspring does not induce the stress response itself but rather is influenced by the broad physiology of the maternal stress response.

Third, psycho-emotional stress is of great relevance to broader psychiatric public health, as *prenatal stress is a common phenomenon*, occurring across maternal age, across the socioeconomic spectrum, and for brief or extended periods of time (Chisholm et al., 2017; Gelaye et al., 2016; Goodman et al., 2014; Goodwin et al., 2017). How maternal stress may influence the developing brain of the offspring is a complex and important area of research. To facilitate the translation of this research into a better understanding of childhood neuropsychiatric risk, we will review here varied aspects of prenatal stress and its interaction with other genetic susceptibilities by comprehensively examining relevant human and animal studies and including a developmental perspective.

Prenatal stress is a difficult variable to measure compared to other exposures which may be more consistently quantifiable. This poses a challenge for understanding mechanisms by which prenatal stress may influence the offspring brain. One factor in this is the often subjective reporting of stress in human studies. Another factor is the contribution of multiple phenomena to stress, including those at the levels of societal, familial, and individual experience. In studies examining connections between prenatal stress and outcomes in offspring, different forms of psychological stress have been assessed including socio-economic status, maternal psychiatric illness and symptoms, and negative life events (Brotnow et al., 2015; Field, 2011; Pluess et al., 2010). The physiological factors that arise from stress and could influence offspring *in utero* are not well understood, but may overlap across these different forms of stress, leading to overlapping outcomes. Research in this area is necessary in order to find better ways to measure stress that will be useful for better-designed studies but also for clinical assessment.

Both prospective and retrospective studies have demonstrated that behavioral problems in children and adults may be more severe or occur more frequently after exposure to prenatal maternal stress. For example, in some studies prenatal maternal stress increases the likelihood of schizophrenia diagnosis, predicts worse Tourette syndrome and attention deficit hyperactivity disorder (ADHD) symptoms, and is more frequent in ADHD cases than typically-developing controls (Malaspina et al., 2008; Motlagh et al., 2010; Zhu et al., 2015). There are a number of other studies that have not found significant associations with these outcomes (Abel et al., 2014; Oerlemans et al., 2016), demonstrating the complexities of this potential risk factor. Prenatal maternal stress may also be associated with an increased risk for depression (Pearson et al., 2013; Plant et al., 2015) and anxiety (Bergman et al., 2007) across childhood and early adulthood. Increasing complementary evidence from work with animal models demonstrates that prenatal stress may causally increase neuropsychiatric risk. The epidemiological patterns in prenatal stress studies which demonstrate different outcomes between distinct populations (Modabbernia et al., 2017; Rice et al., 2010) mirror the variability in studies of genetic risk for many neuropsychiatric diseases (Halldorsdottir and Binder, 2017). The conclusions drawn from genetic studies have focused on multi-hit hypotheses (Mascheretti et al., 2017; Zeng et al., 2016) with interactions between various genetic and environmental risk factors required for clinically significant symptoms.

There has been a great deal of focus in the past fifteen years on psychological stress not occurring prenatally but during childhood, adolescence, and adulthood potentially interacting with genetic risk factors resulting in neuropsychiatric disorders (Enoch, 2012; Sharma et al., 2016; Wermter et al., 2010). The investigations in this area have found a wide range of results, from no interactions to inconclusive interactions with postnatal stress. Others have indicated the presence of gene-environment interactions that may help elucidate mechanisms. Some examples of specific findings with particular relevance to prenatal stress are summarized here. Across studies of both early and later life stress exposure, among the most studied and replicated genetic variants contributing to risk for depression and anxiety in combination with stress are those that encode the serotonin transporter (5-HTT or SERT), the glucocorticoid receptor related gene, *FKBP5*, and brain derived neurotrophic factor (BDNF) (Comasco et al., 2013; Scheuer et al., 2016). A seminal early finding indicates that cortisol reactivity in adult men was only increased in the setting of increased adult life stress *and* a genotype with two short alleles of the serotonin transporter gene (*5-HTTLPR*), linked with lower transporter expression and function and less serotonin clearing (Alexander et al., 2009). A body of work examining the serotonin transporter (*5-HTTLPR)* gene and early life stress has found evidence for interactions (Heiming et al., 2011). Changes based on stress and *5-HTTLPR* genotype in the hippocampus in some studies, in turn, predicted risk for depressive-like symptoms (Carola and Gross, 2012). Other more recent work has suggested that variation in a glucocorticoid receptor related gene, *FKBP5*, moderated the stress of peer-based social victimization in adolescent girls (VanZomeren-Dohm et al., 2015). Much of the evidence for these interactions has arisen from candidate gene studies, but unbiased screens in genome-wide studies are now being performed to determine which genetic risks may be the most significant.

This large body of work has demonstrated that examining multiple risk factors, and particularly the interaction between genes and the stress response with its multiple downstream pathways, can elucidate mechanisms more substantially. These mechanisms may be distinctly different depending on developmental stage, underscoring the importance of understanding the *in utero* environment, central to the interaction of genetic risk, psychological stress, and risk for neuropsychiatric illness. We comprehensively searched the literature on human studies of prenatal stress, and review and summarize (Table 1) all studies examining prenatal stress and genetic risk here. This body of work includes studies examining prenatal stress from cumulative stressors or stressful life events, diagnosis with or symptoms of depression or anxiety, stress self-ratings, bereavement stress, and a comprehensive prenatal stress index. Some key implications of these studies are the complexity of assessing stress through maternal psychiatric symptoms during pregnancy, the importance of maternal genotype, and the significant negative findings related to stress hormone and oxytocin-related genes. As can be appreciated from the further detailed discussion of these human studies in Section 2, multiple lines of research come together to demonstrate the complex interaction of biology, genetic endowment, and the prenatal environment. Collectively, these studies subserve the goal of furthering scientific understanding of the etiology of neuropsychiatric illnesses (Fig. 1).

1.2. Prenatal stress and neurobehavioral alterations in preclinical models

Insight into prenatal stress has also arisen from animal models with ethologically valid stressors such as restraint under bright light, nest manipulation, and predator stimuli that induce similar behavioral and physiological changes in rodents as in humans under stress (Beydoun and Saftlas, 2008; Newport et al., 2002; Patin et al., 2005). A robust literature indicates that prenatal stress experiences of these kinds alter rodent offspring anxiety-like behavior, learning and memory, and stress regulation (Laloux et al., 2012; Lemaire et al., 2000; Van den Hove et al., 2005; Weinstock, 2008) paralleled by altered hippocampal gene expression, cortical inhibitory neuron subtypes (Neeley et al., 2011; Uchida et al., 2014; Wu et al., 2007), and hypothalamic-pituitary-adrenal (HPA) axis response or cortisol reactivity (Glover et al., 2010). Rodent studies have been more likely to demonstrate clear outcomes