Review

Biological Psychiatry

# Germ Cell Origins of Posttraumatic Stress Disorder Risk: The Transgenerational Impact of Parental Stress Experience

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**ABSTRACT**

Altered stress reactivity is a predominant feature of posttraumatic stress disorder (PTSD) and may reflect disease vulnerability, increasing the probability that an individual will develop PTSD following trauma exposure. Environmental factors, particularly prior stress history, contribute to the developmental programming of the hypothalamic-pituitary-adrenal stress axis. Critically, the consequences of stress experiences are transgenerational, with parental stress exposure impacting stress reactivity and PTSD risk in subsequent generations. Potential molecular mechanisms underlying this transmission have been explored in rodent models that specifically examine the paternal lineage, identifying epigenetic signatures in male germ cells as possible substrates of transgenerational programming. Here, we review the role of these germ cell epigenetic marks, including posttranslational histone modifications, DNA methylation, and populations of small noncoding RNAs, in the development of offspring stress axis sensitivity and disease risk.

*Keywords:* Animal models, Epigenetics, HPA axis, PTSD, Stress, Transgenerational

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Posttraumatic stress disorder (PTSD), an anxiety disorder triggered by exposure to a severe traumatic event, presents in only a subset of individuals who experience such a stressor (1). Individual differences in stress sensitivity, primarily regulated by the hypothalamic-pituitary-adrenal (HPA) neuroendocrine stress axis, may be an underlying component of this variability in disease risk (2). In fact, disruption of stress neurocircuitry has been characterized as a pretrauma vulnerability that increases the probability of developing PTSD, rather than a symptom that develops in response to a stressful experience (3). In particular, PTSD has been associated with a unique stress response profile, including low levels of plasma cortisol and increased noradrenergic and adrenergic activity, although these findings are not universal (4). The development of stress reactivity, and its potential consequences on PTSD predisposition, occurs through a dynamic interplay of genetic and environmental factors (5). The role of the environment has been increasingly emphasized, with prior stress exposure highlighted as one of the strongest contributors to later stress sensitivity and PTSD presentation (6).

The behavioral and neuroendocrine consequences of stress exposure, as well as an increase in PTSD risk, have been observed not only in individuals directly exposed to stress but also in their children (7). Potential mechanisms of this experience-dependent transgenerational transmission or the reprogramming of offspring behavior and physiology in response to the parental environment have been investigated in rodent models (8). Studies investigating maternal or paternal experience occurring before offspring conception, so-called lifetime exposures, suggest that transmission occurs through an epigenetic reprogramming of germ cells (9–13). In this review, we focus on these parental lifetime stress experiences and their consequences on subsequent generations' stress reactivity in both humans and animals, and we consider potential molecular mechanisms of transmission, highlighting the role of germ cell epigenetic marks and how these signatures may alter offspring development to confer disease risk or resilience. While maternal stress during pregnancy also impacts offspring stress responses, such experience likely does not rely on germ cell reprogramming and has been expertly reviewed elsewhere [see (14,15)] and thus will not be included in our discussion.

## PARENTAL STRESS AND PTSD RISK

Epidemiological studies have offered strong evidence supporting altered offspring stress reactivity and neuropsychiatric disease risk following maternal or paternal lifetime stress exposure. For instance, adult children of Holocaust survivors were more likely to be diagnosed with a psychiatric disease such as depression, anxiety, and PTSD (16–18), and offspring disease risk was found to increase similarly following parental exposure to abuse or war-related trauma (19–22). In these studies of parental lifetime stress experience, offspring disease risk may have increased as a consequence of offspring HPA stress axis reprogramming (23–25). In fact, maternal PTSD among Holocaust survivors has been associated with increased offspring sensitivity to glucocorticoid stress



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hormones, as well as with decreased methylation of their glucocorticoid receptor NR3C1 promoter region, both of which correlated with their PTSD risk (7,26). Notably, the association between parental stress and offspring PTSD may be driven more by the presentation of parental pathology than by the initial parental trauma event (7), suggesting that the stress of chronic disease may also be required to induce offspring neurodevelopmental reprogramming.

Retrospective human studies have historically emphasized parental behavior as the primary mechanism by which lifetime stress experience can alter offspring stress reactivity and mental health (27–29). They have proposed that disease or prior stress exposure alters parent-child relationships so as to increase the level of stress experienced by offspring and thus impact disease presentation, drawing on the well-known relationship of early life stress with later stress axis dysregulation and PTSD risk (30–34). Interestingly, the impact of early childhood experiences has also been characterized as bidirectional, where healthy parental bonding, defined as the perception of low parental control and high affection, has been associated with lower PTSD risk (35). However, the contribution of alternative mechanisms of transgenerational transmission should be considered alongside the role of experience-dependent changes to parental behavior. Though not yet investigated following parental lifetime stress in humans, exposure to smoking and other environmental toxins has been associated with epigenetic changes in mature sperm, suggesting that molecular signatures in germ cells in addition to parental behavior may be poised to pass on information about the parental environment to their offspring (36,37). The initiation of large-scale longitudinal studies, such as the Avon Longitudinal Study of Parents and Children that has followed approximately 14,500 English children from before birth into adulthood, offers the exciting opportunity to estimate the relative contributions of genetic, behavioral, and epigenetic factors in human transgenerational transmission (38–40).

## ANIMAL MODELS OF LIFETIME STRESS EXPOSURES

The first evidence of the transgenerational effects of parental lifetime stress experience in an animal model was reported nearly half a century ago, where exposure of adult female rats to stress before mating altered offspring behavioral stress responses, increasing exploratory behavior in a novel environment through two subsequent generations (41). In the years since, significant progress has been made in understanding mechanisms by which parental experience reprograms offspring stress-related behaviors and physiology, afforded by extensive evidence of offspring reprogramming in response to parental lifetime stress. For example, in our model of early prenatal stress, exposure to chronic variable stress in utero increased male HPA stress axis reactivity and altered male stress coping behaviors, including increased immobility in the tail suspension test, and these phenotypes transmitted to the next generation through the male lineage (9,42). Postnatal stress has also been shown to induce stress dysregulation in subsequent generations, including observations of behavioral deficits on the forced swim task and decreased blood glucose in response to acute restraint in first and second generation offspring of male mice exposed postnatally to unpredictable maternal separation with maternal stress (10,13,43,44). Notably, the transgenerational impact of parental lifetime stress is not restricted to the perinatal window and changes in offspring stress-related behavior and physiology have been reported following parental exposure stress through adolescence or in adulthood (12,45,46). For example, in our lab, male exposure to chronic variable stress either over the pubertal window or only in adulthood programmed a blunted HPA stress axis response in male and female offspring, a stress phenotype reflecting that observed in PTSD (11). While sex-specific effects reported in some rodent models offer the intriguing possibility that parental experience contributes to sex differences in stress responsivity and in humans, disease risk, the absence of these effects in other models contrasts this hypothesis. Further study of behavioral and physiological phenotypes in both male and female offspring will clarify potential sex-specific vulnerabilities as well as mechanisms by which they may be programmed.

Potential modes of transgenerational transmission have been investigated in rodent models specifically examining the paternal lineage, where the relative exclusion of behavioral and environmental factors affords the mechanistic evaluation of epigenetic marks in sperm, a readily accessible tissue (47). By contrast, transmission through the maternal lineage relies on the complex maternal-fetal/neonatal interaction, where changes in the intrauterine environment, parturition, lactation, and early maternal care may impact stress sensitivity in future generations (48). Few studies have investigated animal models of maternal stress exposure before offspring conception (12,49), likely due to the confounding effects of the maternal milieu and behavior. Additionally, evaluation of potential epigenetic marks in these studies would require superovulation, a hormone-dependent process that may itself change marks in oocytes (50).

In paternal stress studies, epigenetic signatures in sperm have been highlighted as a likely substrate of offspring reprogramming (11,13,51), supported by evidence of altered patterns of retained histone modifications, DNA methylation, and/or populations of small noncoding RNAs in germ cells following diverse paternal insults (52–58). Though behaviorally mediated mechanisms of transmission have been proposed in paternal studies, such as potential shifts in maternal investment in response to a perception of mate quality or the role of paternal behavior (59,60), laboratory rodents typically are not bi-parental. Male rodents do not participate in rearing offspring, and male-female interactions can be limited to defined breeding windows to control for confounding effects of the male rodent's impact on the dam (47). Further, artificial reproductive techniques including in vitro fertilization and zygote microinjection have been used to directly assess epigenetic transmission through the male germ line, demonstrating the role of sperm epigenetic marks in transgenerational reprogramming (13,45,55). Recent development of enzymes capable of site-specific epigenetic modification may offer additional opportunities to investigate the role of specific epigenetic signatures in the sperm in the transgenerational transmission of paternal stress experience (61,62).

## EPIGENETIC SIGNATURES OF STRESS EXPERIENCE

Three modes of epigenetic inheritance in male germ cells—posttranslational histone modifications, DNA methylation, and