Intergenerational transmission of trauma effects: putative role of epigenetic mechanisms

World Psychiatry Official Journal of the World Psychiatric Association
Volume17, Issue3 October 2018 Pages 243-257

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https://onlinelibrary.wiley.com/doi/full/10.1002/wps.20568

Abstract

This paper reviews the research evidence concerning the intergenerational transmission of trauma effects and the possible role of epigenetic mechanisms in this transmission. Two broad categories of epigenetically mediated effects are highlighted. The first involves developmentally programmed effects. These can result from the influence of the offspring's early environmental exposures, including postnatal maternal care as well as *in utero* exposure reflecting maternal stress during pregnancy. The second includes epigenetic changes associated with a preconception trauma in parents that may affect the germline, and impact fetoplacental interactions. Several factors, such as sex-specific epigenetic effects following trauma exposure and parental developmental stage at the time of exposure, explain different effects of maternal and paternal trauma. The most compelling work to date has been done in animal models, where the opportunity for controlled designs enables clear interpretations of transmissible effects. Given the paucity of human studies and the methodological challenges in conducting such studies, it is not possible to attribute intergenerational effects in humans to a single set of biological or other determinants at this time. Elucidating the role of epigenetic mechanisms in intergenerational effects through prospective, multi-generational studies may ultimately yield a cogent understanding of how individual, cultural and societal experiences permeate our biology.

There is now converging evidence supporting the idea that offspring are affected by parental trauma exposures occurring before their birth, and possibly even prior to their conception.

On the simplest level, the concept of intergenerational trauma acknowledges that exposure to extremely adverse events impacts individuals to such a great extent that their offspring find themselves grappling with their parents' post-traumatic state. A more recent and provocative claim is that the experience of trauma – or more accurately the effect of that experience – is "passed" somehow from one generation to the next through non-genomic, possibly epigenetic mechanisms affecting DNA function or gene transcription1-6.

Although both intergenerational (from F0 to F1) and transgenerational (from F0 to F3 or F4) transmission of environmental adversity effects have been

established in animal models, studies in humans have not yet demonstrated that the effects of trauma are heritable through non-genomic (i.e., epigenetic) mechanisms. Nonetheless, there has been much excitement about, and even premature promulgation of, the idea that those effects are transmitted through DNA modifications, explaining the impact of familial experience[7].

The inclination to attribute offspring effects to epigenetic mechanisms in part reflects the inexact and varied use of the term “transmission”. The original use was descriptive, and without mechanistic inferences. Now that animal research has defined a molecular pathway through which transmission of trauma effects might occur, more precise language is warranted to distinguish between clinical observation and biological mechanism. At the current time, the idea that epigenetic mechanisms underlie clinical observations in offspring of trauma survivors represents a hypothesis to be tested.

This review delineates potential epigenetic mechanisms that might be examined in relation to offspring effects, and provides insight into the type of studies that might be most informative.

THE ORIGIN OF STUDIES OF INTERGENERATIONAL TRAUMA EFFECTS

The concept of intergenerational trauma was introduced in the psychiatric literature through descriptions of behavioral and clinical problems in offspring of Holocaust survivors[8].

In a pivotal paper describing three patients who presented for psychiatric treatment, Rakoff[8] wrote: "The parents are not broken conspicuously, yet their children, all of whom were born after the Holocaust, display severe psychiatric symptomatology. It would almost be easier to believe that they, rather than their parents, had suffered the corrupting, searing hell”.

This initial report generated mostly negative reactions, including caution about generalizing from what might have been idiosyncratic observations in a small number of extreme cases[9]. Some stakeholders may have felt that the suggestion that surviving the trauma of genocide had deleterious implications for progeny was stigmatizing in the face of the emerging cultural narrative regarding the Holocaust, which was one of survival against all odds, resilience, and defiance in the hope of preventing such occurrences in the future[10].

The initial anecdotal report, and the reactions to it, generated much empirical research on the question of whether and how Holocaust offspring, conceived and born after World War II, were affected. Hundreds of articles appeared, beginning in the 1970s and continuing for some decades thereafter. The studies described in these reports either failed to find effects in Holocaust offspring, corroborated earlier clinical descriptions, attempted to restrict the observations of damaging effects to a subgroup, or pointed to serious methodological challenges in attempting to address this question empirically[11-13].

A wide range of phenomena was described in studies reporting behavioral difficulties in Holocaust offspring. These included: feelings of over-identification and fused identity with parents, impaired self-esteem stemming from minimization of offspring's own life experiences in comparison to the parental trauma, tendency towards catastrophizing, worry that parental traumas would be repeated, and behavioral disturbances such as experiencing anxiety, traumatic nightmares, dysphoria, guilt, hypervigilance and difficulties in interpersonal functioning. Such studies often did not account for parental psychopathology, but assumed it on the basis of parental exposure.

Similar types of symptoms were later described in the children of Vietnam veterans[14, 15], a phenomenon that was termed "secondary traumatization"[16]. This concept did not imply an intergenerational transmission, but rather referred to the stressful nature of living with a traumatized individual who may be expressing symptoms and recounting or reliving horrific experiences[17].

In the absence of biological mechanisms to explain the reported findings, explanations were almost exclusively psychodynamic or behavioral. For example, it was suggested that trauma survivors externalized their post-traumatic symptoms through their nonverbal behaviors and unconscious reenactments of fear and grief, such that the child became a container for the unwanted, troubling experiences of the parent[18, 19].

Distinctions between "transmission" from parent to child in which the disturbance in the child was a direct consequence of a psychiatric condition in the parent versus an effect reflecting the child's reaction to symptoms in parents[11, 20] were made carefully in order to avoid misattributing offspring effects to earlier parental trauma exposures. Other perspectives – including family dynamics, attachment theory, social psychology and learning theory – were also brought to bear[11, 21-24].

One the most provocative observations regarding Holocaust offspring was the report that Yom Kippur war veterans were more likely to develop post-traumatic stress disorder (PTSD) in response to combat if they had a Holocaust survivor parent[25]. A higher prevalence of PTSD, mood and anxiety disorders was also observed in Holocaust offspring, largely selected from a convenience sample of people seeking treatment for Holocaust-related problems, compared with controls[26]. These findings were replicated in a study assessing the relationship between PTSD in offspring and their own parents, assessed directly by clinical interview of the parent (s)[27].

The increased prevalence of PTSD in Holocaust offspring in response to their own traumatic exposures was later found to be associated with maternal PTSD in Holocaust survivors[28]. Although PTSD was found to occur in association with paternal PTSD in a study of Australian Vietnam Veterans and their offspring[29], the contribution of potential maternal symptoms, even through secondary traumatization, was not assessed. It is rare to identify a cohort in whom both mothers and fathers had similar exposures to an extreme trauma, or even a cohort in whom the impact of lifetime trauma was evaluated in both

parents, and even rarer to have the opportunity to evaluate psychiatric morbidity in both parents and adult children.

While some aspects of intergenerational trauma effects remain contested, discussions about whether there are clinically observable intergenerational effects in offspring have become less contentious in the last several years, with the increasing recognition of the universality of this phenomenon.

Presently, there are discussions about the impact of historical events such as colonization, slavery and displacement trauma in many cultures, including First Nations and native American communities[30, 31], African Americans[32, 33], Australian aboriginals and New Zealand Maori[34, 35], as well as in societies exposed to genocide, ethnic cleansing or war, such as Cambodians[36, 37], Armenians[38, 39], Rwandans[40, 41], Palestinians[42], and communities in the former Yugoslavia[43]. There is also a growing literature about offspring effects following early maternal childhood maltreatment[44-47].

The intense focus on intergenerational effects in these different groups suggests that this topic has broad resonance and global applicability, and provides a mandate for increased attention to this area, including prospective, longitudinal studies that can be designed in the future to determine the mechanisms underlying this phenomenon.

THE INTRODUCTION OF BIOLOGICAL RESEARCH INTO THE STUDY OF INTERGENERATIONAL EFFECTS OF TRAUMA

Research addressing putative biological correlates of intergenerational effects began in the late 1990s[48]. The findings of an increased prevalence of PTSD among offspring with parental PTSD[25, 27] raised the possibility that Holocaust offspring might have specific biological risk factors for PTSD and/or other trauma-associated mood and anxiety disorders, particularly following their own traumatic exposures. The introduction of biology into the debate about intergenerational trauma was a natural outcome of developments in the emerging field of the neurobiology of PTSD, that was beginning to clarify similar issues about the nature and long-term impact of trauma exposure[49].

The initial focus of these studies was on the hypothalamic-pituitary-adrenal (HPA) axis, for several reasons. First, the HPA axis is vulnerable to environmental perturbations. The initial hypothesis with respect to Holocaust offspring was that parental experiences might alter the regulation of stress-related pathways early in development. This idea was plausible, since the HPA axis is subject to early developmental programming[50, 51]. Furthermore, dysregulation of stress neurocircuitry is a fundamental feature of mood and anxiety disorders[52-54], including PTSD, found to be prevalent in offspring. Finally, there had been directionally interesting findings of low cortisol and increased glucocorticoid receptor (GR) sensitivity in Holocaust survivors and other trauma exposed individuals with PTSD, suggesting that the experience of

trauma might leave long-lasting biological signatures in stress-related biology that could be a catalyst for longer-term adaptations[55].

As this work developed, advances in molecular biology, including an understanding of gene-environment interactions and the contribution of environmentally-induced changes in epigenetic regulation of HPA-related genes, provided the tools for examining how salient events could result in enduring, transformative, and possibly even inherited change, laying the groundwork for future molecular studies[56-59].

Studies published over the next decade demonstrated that, in the absence of their own traumatic exposures, offspring of Holocaust survivors were more likely to show HPA axis alterations associated with PTSD, such as lower cortisol levels and enhanced GR responsiveness[60-64]. Observations in offspring whose parents were exposed to other traumatic experiences accorded with these findings. For example, lower cortisol levels were observed in the adult offspring of combat veterans with PTSD compared to offspring of combat veterans without PTSD[65].

Subsequent investigations documented that maternal and paternal PTSD were associated with different biological outcomes. A *post-hoc* analysis of cortisol circadian rhythm data indicated that lower cortisol levels in adult Holocaust offspring were associated with maternal, but not paternal, PTSD[61]. In another study, several measures of GR sensitivity were found to be directionally different in offspring of mothers vs. fathers with PTSD[63]. Specifically, maternal PTSD was associated with lower urinary cortisol levels as well as greater GR sensitivity as measured by the lysozyme inhibition test (an *in vitro* measure of that sensitivity in peripheral tissue) as well as the dexamethasone suppression test (DST). An interaction of maternal and paternal PTSD on urinary cortisol and the DST demonstrated a decreased glucocorticoid sensitivity in offspring with paternal, but not maternal, PTSD.

Initial theories posited that offspring biological effects were reflections of their own experiences as a result of having traumatized parents who may have been symptomatic, neglectful, or otherwise impaired in parenting[11, 21-25]. Differences in offspring effects based on parental gender could similarly be viewed through the lens that mothers and fathers might be associated with different types of parenting roles and behaviors. Thus, in essence, having a traumatized mother, father, or both constituted an early environmental experience that impacted the offspring. Supporting this idea were findings that Holocaust offspring reported higher levels of childhood trauma exposure than demographically similar comparison subjects, particularly if one or more parent had PTSD[66]. In fact, the low cortisol in offspring was found to be associated with offspring reports of emotional abuse[66]. By then it had been established that early childhood maltreatment in itself could result in lower cortisol levels[67-71].

Investigations of younger offspring of mothers who had themselves experienced abuse as children also demonstrated effects on cortisol levels. In one study,

cortisol levels were found to be lower in the offspring of mothers with childhood maltreatment as well as bipolar disorder[72]. Lower cortisol and blunted cortisol reactivity were present in preadolescent boys and girls with maternal PTSD, even after controlling for youth traumatic event history and mental health symptoms[73]. A blunted cortisol reactivity to stress was observed in even younger offspring, toddlers aged 12-48 months, in association with maternal PTSD occurring as a result of interpersonal violence[74]. Infants of women exposed to maternal child abuse also displayed lower baseline cortisol when examined at 6 months of age[44].

Investigators also examined markers other than HPA axis parameters. One study reported that children of mothers exposed to childhood trauma, particularly emotional abuse, had higher sympathetic nervous system activation, which might be a marker for vulnerability to anxiety, compared to children of mothers with low emotional abuse, an effect that remained significant after accounting for maternal PTSD and depression, and for child trauma exposure[45]. In another study, maternal exposure to child abuse was associated with smaller intracranial volume, due to differences in cortical gray matter, in newborns examined within two weeks of birth[75]. This effect was reported to be independent of some potential confounding variables, such as maternal socio-economic status, obstetric complications, obesity, recent interpersonal violence, pre- and early postpartum stress, gestational age at birth, infant sex, and postnatal age at magnetic resonance imaging scan.

As studies begin to examine offspring prospectively, starting in close proximity to their birth, it will be easier to identify the relative contributions of preconception, *in utero*, and postnatal influences on offspring[76]. Indeed, part of the difficulty in studying adult offspring of trauma survivors, particularly retrospectively, is that it is difficult to make attributions about the origin of any observed biological manifestation. Such explorations must also invariably include the contribution of genotype, as it is becoming increasingly recognized that at least some "programmed" epigenetic modifications may be established through gene x environment effects[5, 7]. Indeed, such interactions may help explain diversity in offspring responses to parental trauma effects.

POTENTIAL MECHANISMS FOR OBSERVED BIOLOGICAL EFFECTS IN OFFSPRING OF TRAUMA SURVIVORS

The first basic science approach to understanding offspring effects was the work of Meaney et al[77, 78], beginning in the late 1980s. This team of researchers initially focused on long-term effects of early handling of rat pups, using a model in which mothers were separated from their neonatal pups for several minutes each day. In adulthood, the handled rats had altered basal and stress-induced corticosterone levels as well as higher GR sensitivity on the low-dose DST and greater GR number in the hippocampus[77-79].

However, it subsequently became clear that the observed effects in offspring were mediated not by the maternal separation or the early handling by humans, but rather by the behavior of the mother upon being reunited with her pups in

the home cage, specifically the extent of licking and grooming of pups. The offspring of mothers that displayed lower vs. higher licking and grooming demonstrated distinct neuroendocrine and behavioral parameters, which persisted from F1 to F2[80, 81].

This clear example of developmental programming, in which postnatal exposures in the pups (i.e., variations in maternal licking and grooming behavior) induced enduring changes in behavior and HPA axis responsiveness, seemed relevant to the offspring of trauma survivors[82]. Interestingly, the neuroendocrine phenotype of Holocaust offspring with maternal PTSD was more consistent with maternal overprotection than neglect, as low cortisol levels in offspring were found to be associated with overprotection[83]. Maternal overprotection subsequent to stress exposure was also reported in association with low cortisol/dehydroepiandrosterone (DHEA) ratio in offspring[84].

In 2002, a seminal paper demonstrated that the rat offspring effects of licking and grooming were associated with an epigenetic change, namely, DNA methylation at a GR (nr3c1) gene promoter in the hippocampus[85, 86]. Later work expanded this finding from epigenetic marks at a single gene promoter on one gene to clustered epigenetic changes in promoters associated with transcriptional activity across broad genomic areas[87-89]. The effects in adulthood were determined to be directly related to the early postnatal environmental exposures to variations in maternal care, since they were prevented by cross-fostering neonatal rat pups to mothers displaying different behavioral characteristics[81, 86, 90, 91]. The elimination of offspring effects through cross-fostering is a potent example of social transfer of information through parental behavior – not parental DNA or biological inheritance. Yet these findings constituted a powerful example of how early environmental inputs and parental behavior could affect offspring DNA methylation, behavior, and the function of neuroendocrine stress responsiveness for more than one generation.

It is hard to overstate the level of excitement generated by the findings demonstrating an epigenetic alteration in brain in response to variations in postnatal maternal care. Though epigenetic mechanisms and their central role in development had been known since the 1940s, following C. Waddington's initial descriptions of these molecular mechanisms[92], these concepts had not been previously applied as explanations for how environmental exposures – such as parental behaviors – could reprogram stress hormone biology, affecting brain and behavior of progeny[93, 94].

This elegant series of studies provided a clear molecular link between maternal behavior and gene function in offspring, mediated by epigenetic mechanisms, and producing functional biological correlates in endocrine and behavioral measures related to stress reactivity[95, 96]. Meaney et al's work also made clear the possibility that epigenetic effects could occur at various stages throughout life, potentially influencing risk and vulnerability for chronic responses to trauma, such as PTSD, across the lifespan[82, 97-101].

RELEVANCE OF EPIGENETIC MECHANISMS TO INTERGENERATIONAL EFFECTS

The term "epigenetics" refers to a set of potentially heritable changes in the genome that can be induced by environmental events. These changes affect the function of genomic DNA, its associated histone proteins, and non-coding RNAs, collectively referred to as chromatin, but do not involve an alteration of DNA sequence[102-104].

Of the many mechanisms of epigenetic regulation that have been described, DNA methylation at the cytosine site has been the best characterized in the mammalian genome[105, 106]. Other regulators of chromatin include post-translational modification of histones and accompanying RNA-signaling as well as higher order changes in nucleosome organization[102].

Epigenetic modifications impact gene function by altering gene regulatory elements that affect the action of gene transcription factors[91]. Generally, methylation within specific regions of the gene is an efficient way of gene silencing and provides a molecular mechanism for the occurrence of gene-environment interactions independent of a specific genetic marker or gene version[107]. However, the actual contribution of genetic influences on environmentally-induced events has been insufficiently studied.

The impact of an epigenetic change on gene function is determined by the specific nature and location of an epigenetic mark on the gene and its proximity to the transcription start site, and possibly other genomic regulatory regions of interest[107-112]. It is not a trivial matter to determine the location on a gene, or within the genome, that would activate the relevant transcription factors which result in phenotypic change. The work of Meaney et al established a molecular mechanism for postnatal glucocorticoid programming, and identified the regions within the GR gene promoter that result in long-lasting changes in the biological systems associated with stress response in offspring[91, 113].

Subsequent studies have built on this information by examining the 1F exon promoter, a relatively small area of the GR gene[57, 114-120]. In fact, there may be numerous other areas of interest on the GR and other genes that have yet to be identified.

TRANSLATIONAL STUDIES LINKING EPIGENETIC FINDINGS ASSOCIATED WITH MATERNAL CARE IN ANIMALS TO CHILDHOOD ADVERSITY AND OFFSPRING EFFECTS IN HUMANS

The first documented study of the GR promoter in humans showed higher methylation of the hippocampal GR 1F promoter in post-mortem tissue of adult suicide victims with a history of childhood abuse, similar to findings in rodent pups raised by mothers who provided low levels of licking and grooming[121, 122]. The findings in human brains of abuse victims implied that early developmental traumas such as those perpetrated by primary caretakers might

influence the same neurobiological developmental systems as those involved in early maternal care[121].

Following this observation in post-mortem brain tissue, higher GR promoter methylation in circulating leukocytes of healthy adults was also found to be associated with disrupted, inadequate, or abusive parenting[123-125].

The above work provided a strong rationale for the examination of the GR promoter methylation in peripheral blood mononuclear cells of Holocaust offspring. In parallel with the neuroendocrine observations, the results of these analyses indicated a significant interaction of maternal and paternal PTSD on GR gene methylation[126]. The interaction demonstrated that, in the absence of maternal PTSD, offspring with paternal PTSD showed higher GR promoter methylation, whereas offspring with both maternal and paternal PTSD showed lower methylation of this promoter region. Lower GR 1F promoter methylation was significantly associated with greater GR sensitivity, as indicated by greater post-dexamethasone cortisol suppression. Furthermore, a clustering analysis of clinical self-report scales revealed that maternal and paternal PTSD were associated with different clinical indicators as well. Together, the data suggested that there are likely to be different underlying mechanisms for the intergenerational effects on offspring biology and behavior depending on parental gender and PTSD status.

Some findings in offspring, however, have not been directly linked with parental gender and PTSD status, in some cases because the small sample size prohibited such analysis. For example, a preliminary study examining FKBP5 intron 7 methylation in Holocaust survivors and their children demonstrated alterations at the same site within intron 7 in both parents and their children, with no specific consideration of parental gender or PTSD[127]. The FKBP5 gene encodes a protein that functions as a co-chaperone of the bound cortisol-glucocorticoid complex in the cell nucleus[128]. FKBP5 methylation in parents and their children were positively correlated. However, interestingly, they were directionally distinct (when compared to their respective control groups), with Holocaust offspring showing lower methylation at this site compared to demographically-matched controls, and Holocaust survivors demonstrating higher methylation compared to respective controls.

It is important to note that effects of parental behavior should not be conflated with directly "inherited" effects resulting from biological transmission from parent to child, even though both may be associated with epigenetic findings. Epigenetic mechanisms are operational throughout life and are highly responsive to environmental perturbations. It has now been shown that stressful experiences such as adult trauma change methylation of the GR gene in blood cells, whether primed by early experience or not[118, 119, 129, 130].

PRENATAL MATERNAL CONTRIBUTIONS TO OFFSPRING VIA FETOPLACENTAL INTERACTIONS

An emerging body of literature has raised the possibility that maternal effects of trauma exposure might contribute to offspring effects through fetoplacental interactions[131-135]. This possibility is consistent with clinical, neuroendocrine and epigenetic findings, in which maternal and paternal PTSD predicted different psychiatric and biological outcomes in offspring[28, 126].

The intrauterine environment presents a developmentally potent context[95], mechanistically distinct from postnatal parenting or family environment, through which maternal trauma or stressful experiences may influence fetal epigenetic programming of the HPA axis[136]. By 22 weeks of gestation, the fetal HPA axis is developed and functioning, although it continues to be sensitive to environmental influence[137, 138]. The placenta nourishes and protects the fetus, buffering the effects of maternal glucocorticoids through the expression of placental 11B-hydroxysteroid dehydrogenase type 2 (11β-HSD2), an enzyme that converts cortisol to inactive cortisone[139].

In animal models, prenatal stress has been shown to lower expression of 11β-HSD2 mRNA and 11B-HSD2 activity, both of which are associated with increased 11β-HSD2 methylation in the placenta[140]. Such effects of prenatal stress would have profound consequences on fetal exposure to glucocorticoids and the development of glucocorticoid sensitive systems, such as the HPA axis.

The potential for maternal trauma or stress to program fetal development through placental alterations has been explored in animal and human studies, historically with an emphasis on HPA axis markers, but more recently using epigenetic measures[141-145].

The gestational stage of the fetus is an important determinant of the impact of prenatal exposures on offspring, indicative of developmentally sensitive windows of fetal development[146, 147]. The relevance of gestational stage during maternal trauma exposure was highlighted in a prospective study of infants born to mothers who had been pregnant and had to evacuate the World Trade Center during the terrorist attacks on September 11, 2001[146]. Infant offspring demonstrated lower cortisol levels in association with maternal PTSD, particularly if the mother had been exposed to trauma in the third trimester. At 9 months, maternal morning cortisol levels were inversely related to maternal ratings of infant distress and response to novelty. Mothers who had PTSD rated their infants as having greater distress to novelty than did mothers without PTSD[148], and the offspring of mothers with PTSD showed evidence of anxiety and behavioral disturbances.

The relevance of prenatal stage at exposure was also demonstrated by two important epidemiological studies of Swedish and Dutch famines, that identified transgenerational health and disease outcomes in children and grandchildren[149]. Phenotypic and epigenetic changes were observed in adults who were exposed *in utero* to the Dutch famine of 1944-45, but only among those exposed at the time of conception and during the first half of gestation,

compared to those exposed in the third trimester or early postnatal period[150, 151].

More recently, a relatively large epigenetic study of the Dutch hunger cohort (422 exposed and 463 sibling controls) identified alterations in DNA methylation specifically associated with *in utero* exposure to maternal famine[152]. Among those exposed early in gestation, additional CpG mediators were identified. Interestingly, exposure to famine during pregnancy had biological and behavioral effects on grandchildren, such as on adiposity[153]. This transgenerational effect has been attributed to the fact that prenatal exposure directly impacts both the fetus and the fetal germ cells, thus directly exposing the third generation. In a recent study, grandmaternal stress during pregnancy was associated with genome-wide methylation changes in offspring and grandchildren[154].

Studies of preconception exposure to trauma without specific consideration of gestational age of exposure have also been published. A number of smaller studies have identified an association of prenatal maternal trauma with methylation of the NR3C1 gene in offspring. Higher levels of NR3C1 methylation were observed in offspring aged 10-19 of mothers who experienced intimate partner violence during, but not prior to or following, pregnancy[155].

Higher methylation in the promoter of the NR3C1 gene was also observed in newborns of mothers in the Democratic Republic of Congo exposed to severe prenatal stress, with the strongest effect for maternal warzone stress experiences[156], and in the children of women exposed to the Tutsi genocide during pregnancy compared with non-genocide exposed women of the same ethnicity and pregnant at the same time, and their children[41]. Among offspring of women pregnant during the 1998 Quebec ice storm, those whose mothers experienced objective hardship, but not subjective distress, had methylation alterations in genes related to immune function[157]. These findings suggest enduring epigenetic alterations in offspring associated with maternal trauma during gestation.

Given the directionality of these findings, which is consistent with elevated cortisol levels, it may be that exposures in mothers which originate during pregnancy result in directionally different epigenetic alterations from those observed in offspring where the maternal (or paternal) trauma occurred prior to conception. There may also be different effects on offspring, as well mechanisms underlying these effects, depending on the history of trauma exposure and/or psychiatric symptoms prior to pregnancy.

One question that arises from studies of women traumatized prior to or during pregnancy is the extent to which effects on offspring are mediated by psychological symptoms or subjective reactions to adversity. It may be that intrauterine signals which affect fetal biology are driven by maternal symptoms such as anxiety, depression, or hyperarousal. It is certainly plausible that women with early childhood trauma or prenatal trauma exposure might experience pregnancy with ambivalence or distress[76]. Thus, any alteration in

offspring may be mediated by mental health symptoms during gestation, and certainly extend to the postnatal environment. In studies of Holocaust offspring, perhaps the most salient observation has been that most differences in offspring phenotype were associated with persistent psychological effects of parents.

This question can also be partially addressed by considering studies of the effects of mood and anxiety disorders during pregnancy in the absence of trauma exposure. In one study, the effects of prenatal maternal depression on methylation levels in the promoter and exon 1F region of the NR3C1 gene in newborn cord blood identified a trimester effect, with third trimester maternal depression/anxiety associated with higher methylation of NR3C1 at a predicted NGF1-A binding site[141]. Functionally, methylation levels were associated with salivary cortisol stress responses in the newborns at 3 months, indicating that maternal mood and offspring HPA axis reactivity may be linked through epigenetic processes and sensitive to fetal developmental stage. In contrast, a study of pregnancy-related anxiety found that methylation at the 1F exon of the NR3C1 in offspring was influenced by maternal anxiety only during the first two trimesters[158].

FETOPLACENTAL INTERACTIONS: REGULATION BY SEX OF OFFSPRING

One of the most fascinating observations from studies examining the effects on offspring of maternal stress during pregnancy is that prenatal stress has different effects in male vs. female offspring[143, 159-161]. In animal models of prenatal stress, exposure to chronic stress *in utero* increased male, but not female, HPA stress reactivity (e.g., behavioral response to the tail suspension test)[159, 162]. These behaviors were transmitted to the next generation through the male germ line. Among mice exposed to stress during early, mid and late gestation, male F1 with early gestation prenatal stress exposure demonstrated behavioral indicators of stress responsivity and anhedonia, as well as alterations in GR and corticotrophin-releasing factor (CRF) expression and increased HPA axis responsivity, with corresponding alteration in CRF and nr3c1 gene methylation[159].

The importance of fetal sex, or more specifically, trophoblast cells from the embryo reflecting fetal sex, is that it may differentially regulate epigenetic signals in the placenta, leading to differential signaling that feeds back to the offspring[140]. These sex-related placental differences may confer protection or vulnerability to the fetus through differential exposure to maternal stress hormones. For example, early gestational stress exposure led to sex differences

in expression and methylation of genes in the placenta associated with growth and nutrient transport[159].

A recent review of sex differences in HPA axis programming concluded that female offspring exposed to prenatal stressors had higher HPA axis reactivity than did similarly exposed males, with differences in placental expression of 11β-HSD enzymes, but that prenatal stress in humans was associated with alterations in diurnal cortisol secretion in males that were not apparent in females[163]. Thus there may be slightly different effects according to species and sex, depending on the parameter being measured.

While there is a strong suggestion that prenatal maternal effects produce a wide range of behavioral and biological outcomes in offspring, there is still an important need to provide clarification on the different contributions of maternal exposure, including the nature of the exposure, the timing of exposure in pregnancy, the sex of the fetus, the nature of maternal symptoms, or other potentially significant contributions such as nutrition, exposure to toxins, delivery factors, medication effects, socio-demographic variables, and other potential mediators.

In studies where offspring are also examined, it is difficult to break down effects of prenatal exposures from postnatal maternal factors, but studies examining offspring in close proximity to birth may be particularly informative regarding offspring biology. They will be less informative with respect to offspring phenotype as it is expressed later in life.

Studies of prenatal maternal exposures provide incomplete data regarding several other factors that may be relevant to offspring effects. Of particular interest are the potential contributions of preconception trauma in mothers (or fathers) to prenatal influences *in utero*. Preconception trauma exposure, prenatal stress, and postnatal parenting are unlikely to be independent in humans, adding to the complexity of drawing conclusions about specific influences on offspring.

INTERGENERATIONAL EFFECTS OF PRECONCEPTION MATERNAL TRAUMA

It is tempting to assume that findings of preconception trauma, particularly occurring prior to puberty, represent trauma-induced epigenetic changes to the oocyte that are maintained throughout embryogenesis and/or reestablished post-conception, thereby influencing the placental environment findings[164]. There are no studies to date examining this possibility in either animal or human samples. The complexities of examining this issue are obvious, because it is methodologically extremely difficult to separate out effects in an oocyte from effects of the fetoplacental environment. Although all of a female's oocytes are present at birth, they can be affected by environmental exposures, particularly during childhood[165]. Oocytes remain in a haploid de-methylated

state until puberty, and are therefore vulnerable to environmental perturbations[166].

The notion that oocytes may be affected by preconception trauma is consistent with findings in Holocaust offspring in association with maternal age of exposure during the Holocaust. However, this explanation would decidedly be an inference. Maternal age at Holocaust exposure and maternal PTSD were found to independently influence urinary cortisol levels and cortisol metabolism in adult offspring, with the strongest effects in offspring of mothers who were children during World War II[167]. In an unpublished study, earlier age of maternal Holocaust exposure was also associated with lower FKBP5 methylation at intron 7 in offspring.

Such data must be interpreted with caution. Regarding exposures during World War II, including the studies of the Dutch famine, it is difficult, if not impossible, to ascertain exactly when the traumatic period began. The unknown variance associated with unmeasured stress in prior generations and its relevance to any maternal exposures is simply not known and creates a difficulty in ascertaining mechanisms. However, the limited data suggesting an association of an epigenetic alteration with maternal age at trauma exposure imply potential contributions of both *in utero* effects and possibly preconception epigenetic changes to gametes.

The difficulty in parsing different maternal contributors to offspring outcome does not mean that epigenetic changes to oocytes are not potential contributors to offspring phenotype – just that this has not yet been determined, and will require innovative methods of investigation. However, the possibility that trauma-related epigenetic changes in germ cells contribute to offspring phenotype has been demonstrated in association with sperm.

Offspring effects may be mediated, in part, by epigenetic changes in parental germ cells resulting from acquired parental stress exposures throughout life[3], [168]-[170]. Germ cells in both females and males can be affected by trauma exposure, but the critical periods for affecting oocytes and sperm may differ. Accordingly, the nature of the effects may differ in oocytes and sperm in relation to trauma exposure. The extent to which exposure-related changes in germ cells are similar to epigenetic alterations in brain is an area for continued investigation[171], [172].

PRECONCEPTION PATERNAL EFFECTS AND OFFSPRING PHENOTYPE: PROOF OF CONCEPT FOR THE ROLE OF SPERM

A rapidly growing literature has focused on paternal transmission through sperm[3], [173]. Unlike oocytes, which are formed in females prior to birth, spermatogenesis in males is initiated in the testes at puberty and continues throughout the lifespan[174]. Studying transmission through sperm eliminates confounds created by influences of fetoplacental environment, delivery factors, and maternal care as described above. Furthermore, paternal exposure to

preconception stress at any stage of development might impact gametes but, as with females, there may be critical periods of vulnerability to insult.

Among the epigenetic mechanisms that have been implicated in paternal transmission of stress effects via sperm are DNA methylation, oxidative damage to sperm DNA, histone modifications, and changes in small noncoding RNA[175-179], including microRNA[180, 181]. Changes in any of these properties in sperm could affect gene expression and other biological processes in the developing embryo and fetus, setting the stage for phenotypic change in offspring[182]. It is important to note that in cases where such processes then result in modifications of DNA methylation, the process of transmission would remain indirect, despite germ cell mediation. It is the event-related change in germ cell biology that produces the methylation mark, not the original "trauma".

To date, there are no known studies that have directly examined transgenerational effects mediated through sperm in humans. Thus, there is no information about epigenetic changes in sperm of fathers exposed to adversity with examination of potential corresponding changes in the sperm of their sons. However, there have been several observational studies demonstrating that environmental exposures in males – such as famine, obesity, smoking, alcohol consumption, exposure to toxins, and exposure to stress – result in subsequent behavioral and biologic effects in offspring[183-187]. Some of these exposures have also been associated with alterations in sperm of the exposed father. Still, the compelling data demonstrating heritable epigenetic alterations come from animal models[179, 181], supported by an increasing understanding of the intricate details of epigenetic mechanisms associated with mammalian embryology and fetal development.

Contrary to initial understanding, it is now believed that some epigenetic changes in germ cells may survive the nearly global erasure of DNA methylation that occurs before implantation of the embryo, or associate with other epigenetic mechanisms[188, 189]. DNA methylation marks are re-established following their erasure, allowing developmental processes, including cell differentiation, to occur[190]. Some embryonic cells will become germ cells (sperm and oocytes). In primordial germ cells, DNA methylation is again erased and re-established based on the sex of the transmitting parent[190]. Because of a phenomenon called imprinting, maternal and paternal genomes are differentially marked and re-programmed, and a small number of regions from the DNA of the parent of origin may remain with DNA methylation intact[173, 189, 191].

Genomic imprinting patterns can have major effects on the embryonic phenotype[192, 193]. This provides at least one putative mechanism in addition to parent of origin effects for the transfer of an environmentally-induced epigenetic mark from one generation to another. It should be stated, however, that the exact nature of the mechanisms involved in transmission through gametes continues to remain obscure, and knowledge in this area is greatly

expanding, even as such effects are demonstrated in mammalian studies[194-196].

It is of interest to compare effects of fathers who conceived during the Dutch hunger with effects of mothers who may have further influenced the development of the offspring *in utero*. Offspring of F1 fathers, but not F1 mothers, who were prenatally exposed to famine had higher body mass index and obesity rates as adults[197]. In Sweden, limited food supply affected mortality rates of grandchildren in a sex-specific manner through the paternal line. Restricted nutritional intake in paternal grandfathers affected mortality rates in grandsons only, whereas paternal grandmother access to food was associated with mortality of granddaughters. These effects were observed only when limited food access occurred prior to puberty, supporting the hypothesis that the transmission occurred through epigenetic programming of gametes and may be mediated by the X and Y sex chromosomes[181, 195].

There are several observations that exposures of fathers or even grandfathers affect offspring through non-genomic mechanisms of transmission. A three-generational study of obesity in males and females demonstrated different risk and protective factors associated with grandparental and parental food availability during puberty[194]. Overeating in paternal grandfathers was associated with increased risk for diabetes in grandchildren, whereas limited food availability in fathers was associated with protection from cardiovascular death in sons. It was hypothesized that these changes were mediated by nutrition-related transgenerational effects down the male line, involving modifications of the DNA and/or histones in sperm. Interestingly, a reanalysis of these data showed that the child's early life circumstances were also relevant to findings from father to son but, when childhood factors in sons were controlled in statistical analyses, the transmission effects through the male line were strengthened[194].

The extent of paternal alcoholism has also been associated with neurological and behavioral deficits in offspring[198]. Changes in DNA methylation were observed in sperm from men with alcohol or opioid dependence[199, 200], but effects in offspring were not measured. Smoking was reported to increase risk of childhood cancer in the offspring of male smokers[187], and was later found to be associated with reduced sperm count, motility and morphology, and altered sperm microRNA, mitochondria and protein in the smoker parent[201, 202]. Data from the UK Avon Longitudinal Study of Parents and Children study identified effects of paternal smoking on offspring, but only when smoking occurred before puberty[195].

In these cases, it was hypothesized that environmental perturbations within the testes/epididymides led to epigenetic changes in the development or maturation of sperm that were then transferred to the oocyte at fertilization, affecting gene expression of the early embryo or modulating DNA methyltransferases or histone regulators.

In the absence of studies examining the effects of trauma through the male germ line in humans, the above findings demonstrate that a wide range of environmental exposures, not only exposure to extreme trauma, can have biological and behavioral effects that persist in one or more generations. Future studies examining behavioral and epigenetic effects in sperm in relation to pre- and post-pubertal trauma exposure in males and their offspring will greatly shed light on this topic.

STUDIES OF INTER- AND TRANSGENERATIONAL STRESS IN MALE RODENTS

Research on possible intergenerational transmission of stress effects through epigenetic marks in sperm has been conducted in rodents, and includes preconception exposures at various developmental stages to stressful and adverse social experiences[149, 175, 176, 179, 181, 203, 204]. Such studies have produced very compelling data suggesting that exposure to extreme stress in males can affect brain, behavior and sperm in the next generation[176, 179].

In one study, male mice were fear conditioned with an odorant at two months of age (post-puberty but not yet adults)[175]. The odorant acetophenone paired with an electric shock resulted in behavioral sensitivity in the fear conditioned mice, with an accompanying change in DNA methylation in brain and sperm of the M71 receptor, which is involved in sensing acetophenone. An increased size in the M71 specific glomeruli in the olfactory epithelium and bulb was also observed[175]. The offspring (F1) of odor conditioned F0 males mated with naïve females also showed similar changes in brain and sperm. When the F1 males were themselves mated, changes in brain persisted in the F2 male offspring, demonstrating conservation of the effect through two generations.

In vitro fertilization was also used to implant the F0 sperm into a naïve female. This produced similar behavioral and biological findings in the F1, further pointing to biological inheritance through sperm. The *in vitro* fertilization study permitted changes to be attributed to sperm and not, for example, maternal reactions to behavior in the conditioned father during mating, or other potential confounds. To even more carefully eliminate any maternal contributions to offspring effects, a cross-fostering study was performed, which confirmed the absence of maternal effects on the observed offspring phenotype.

This series of studies provides a clear demonstration of an epigenetically mediated transgenerational biological inheritance through sperm of a behavioral trait and corresponding neuroanatomical brain changes that persist for two generations.

A similar observation of transgenerational paternal effects emerged from a different paradigm, in which two groups of male mice were exposed to a wide range of stressors over 42 days at puberty or adulthood[179]. These mice (F0) demonstrated behavioral changes in response to the stressor, and also changes in several specific sperm microRNA. Males were bred with naïve females and

produced offspring with blunted HPA axis responsivity as well as changes in transcription of GR genes in the paraventricular nucleus[179].

These findings confirmed that early or later life exposures in the male mouse can affect germ cell microRNA, and are sufficient to result in a similar phenotype in the subsequent generation, again confirming the transmission through sperm in an independent animal model. This study is noteworthy for examining both male and female F1. Although significant sex differences were noted in endocrine and behavioral measures, there was no interaction between sex and paternal stress in the offspring of those exposed at puberty or adulthood.

An independent research team also demonstrated that small non-coding RNAs (sncRNAs), common in sperm, can mediate inheritance of environmentally acquired traits or phenotypes in mice[176]. Specifically, early life stress, modeled by unpredictable maternal separation and maternal stress, led to depressive-like behavioral patterns upon exposure to novel environments and changes in sncRNAs in F1 sperm. F0 exposed to several unpredictable maternal stressors and separation demonstrated changes that could be observed across two generations[176]. When altered microRNAs from sperm of the stressed males were injected into fertilized wild-type oocytes, comparable behavioral, metabolic and molecular outcomes were observed in the F2 offspring, indicating transmission of epigenetic marks. Furthermore, F3 offspring of these animals continued to show phenotypic differences, indicating conservation of stress effects through sperm.

Importantly, another study demonstrated that environmental enrichment following stress exposure in the F0 could reverse and prevent some of the effects[205]. Early maternal separation resulted in decreased nr3c1 DNA methylation in the hippocampus and sperm cells, as well as poor coping behavior. When environmental enrichment was applied at weaning until adulthood, the behavioral and methylation effects were no longer observed in the F0 or F1. These findings indicate that stress-induced changes to germ cells are not immutable and can be reversed by alternative environmental perturbations that are directed at stimulating plasticity. It is for this reason that environmental effects which cross the generations do not necessarily predict negative generational consequences – posing challenges for interpretation of such effects.

Furthermore, not all stressors impact sperm in an intergenerational manner. For example, in a social defeat model of stress, male and female F1 mice exhibited altered behaviors, and male F1 had a broader range of affected behaviors[204]. However, these results were not observed when offspring were generated by *in vitro* fertilization, implicating behavioral, rather than germ cell epigenetic, influence.

Thus, evidence is beginning to converge around the role of epigenetic mechanisms. However, there is much diversity in effects, and opportunities for modifying even strong effects of non-coding RNAs, chromatin, and DNA

methylation. Future research can delineate the exact nature of the stressors and their sensitivity to reversal through targeted environmental influences designed to enhance resilience[175, 206, 207].

CONCLUSIONS AND FUTURE DIRECTIONS

Scientific studies are rapidly identifying epigenetic mechanisms to explain how an environmental exposure may lead to an enduring change in the function of DNA that can be passed to future generations. This review emphasized two broad categories of offspring effects that may be underpinned by epigenetic mechanisms. The first involve accommodations made by offspring in response to their own environmental exposures in early life, or even *in utero*. These changes are likely to be mediated primarily by maternal trauma-related symptoms, but may be affected by multiple inputs, including paternal trauma-related effects. The second are the effects of a preconception parental trauma that remain in the germ cell and following conception, affecting the offspring's development *in utero* and subsequent postnatal phenotype.

In both cases, the transmission is a result of parental exposure effects. In the context of offspring born to two trauma survivors, these two modes of epigenetic influences are likely to interact, and it is indeed very difficult to parse out the many potential contributions to offspring phenotype, not to mention those related to the offspring's own experiences through childhood, adolescence and adulthood.

Epigenetic mechanisms have been favored over genetic explanations (or gene-environment interactions) of intergenerational effects in part because of their potential to explain the phenotypic differences in offspring associated with maternal vs. paternal trauma exposure. The state of the science in relation to human offspring at present is that, whereas some neuroendocrine and epigenetic alterations have been documented in connection with maternal and paternal trauma exposure and PTSD, studies have not yet conclusively demonstrated epigenetic transmission of trauma effects in humans.

Nonetheless, the findings in animal models implicating epigenetic mechanisms in the transmission of stress effects through germ cells have created much excitement for the possibility that similar mechanisms might be operating in humans. Identifying evidence for these mechanisms will require prospective, longitudinal, and multi-generational studies. Parallel studies in animals will permit a more rigorous elucidation of the effects of specific experiences and mechanisms through cross-fostering and *in vitro* fertilization studies.

Research on epigenetic inheritance of effects of trauma faces many scientific and methodological complexities, not to mention conceptual issues regarding interpretation of transmitted effects. This review has not examined the contribution of genetic factors to trauma-related epigenetic alterations, but future studies should incorporate an understanding of both the genetic and environmental factors that augment or mitigate offspring effects.

Other areas for future studies concern the relevance of age or developmental stage of the parental trauma exposure to offspring effects, as well as the notion that male and female offspring may be differentially affected by maternal and paternal trauma. Moreover, there is a very small, but emerging, literature regarding potential reversal of intergenerational effects and their implications for resilience[205].

At the present time, the field has not sufficiently grappled with the meaning of the intergenerational transmission of trauma effects for the offspring. It could be argued that this transmission is indicative of increased vulnerability. On the other hand, this transmission may extend the adaptive capacities of offspring through a biological preparation for adverse circumstances similar to those encountered by the parent. Ultimately, the potential utility, and possible stability, of an environmentally induced trait transmitted to an offspring will depend on the offspring's environmental context.

This review highlights some of the complexities involved in making inferences about the mechanisms that underlie intergenerational and transgenerational transmission. It is inarguable that people feel affected by the consequences of trauma exposure in previous generations. The assertion that an effect is truly transgenerational requires ruling out direct exposure of offspring as a causal mechanism. Thus, for females, traits must be observed in F3 females to be considered transgenerational, because the F1 female offspring is exposed to the stressor during gestation through the intrauterine environment. This may, in turn, affect programming of the F1 fetus' germline, which would be observed in her F2 offspring. Only the originally exposed mother's F3 offspring would not have been directly exposed to the stressor. In males, F1 may be influenced via the germ line of the exposed F0 father, but since sperm is not generated in the fetus (as ova are in females), transmission of trauma-associated traits to F2 would be considered transgenerational transmission.

These guidelines should be kept in mind as studies on effects of trauma on offspring in the next and subsequent generations are pursued. The concept of intergenerational transmission has resonated among offspring who feel affected by their parents' experience. The concept has also been embraced by communities that are affected by significant traumatic experiences through several generations. That there may be a biological or molecular representation of an intergenerational effect appears to validate the experience of offspring who may feel that they bear effects of their parents' hardship, even if the concept may also carry an implication that they are damaged, impaired, or permanently disadvantaged. It is also important to underscore the lack of permanence of effects once environmental conditions are altered.

Continued research in this field will likely reveal that epigenetically induced changes are a reflection of environmental exposure, and therefore by definition malleable. Even potentially heritable changes can be modified, because environments change. The role of genetics in mediating environmentally induced epigenetic effects remains an important frontier. Regardless, the principle of epigenetic plasticity implies that changes to the epigenome might

reset when the environmental insults are no longer present, or when we have changed sufficiently to address environmental challenges in a new way. It is the ability to flexibly respond to environmental stimuli that is fundamentally adaptive and the basis of human resilience.

ACKNOWLEDGEMENTS

The authors would like to thank L.M. Bierer and M.J. Meaney for their comments and very careful review of this paper, and A. Ropes for assistance with manuscript preparation.

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