Journal of Developmental Origins of Health and Disease (2016), 7(6), 588–601.

doi:10.1017/S2040174416000416
Themed Issue: Developmental Origins of Adult Mental Health and Illness

REVIEW

Transgenerational transmission of pregestational and prenatal experience: maternal adversity, enrichment, and underlying epigenetic and environmental mechanisms

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Transgenerational transmission refers to positive and negative adaptations in brain function and behavior that affect following generations. In this paper, empirical findings regarding the transgenerational transmission of maternal adversity during three critical periods – childhood, pregestational adulthood and pregnancy – will be reviewed in terms of pregnancy outcomes, maternal care, offspring behavior and development, and physiological functioning. Research on the transgenerational transmission of enrichment and the implications for interventions to ameliorate the consequences of adversity will also be presented. In the final section, underlying epigenetic and environmental mechanisms that have been proposed to explain how experience is transferred across generations through transgenerational transmission will be reviewed. Directions for future research are suggested throughout.

Received 30 January 2016; Revised 14 May 2016; Accepted 4 July 2016; First published online 4 August 2016

Key words: adversity, enrichment, epigenetics, prenatal/pregestational, transgenerational

Introduction

Many women experience various forms of psychological, social and environmental adversity, and mounting evidence indicates that the consequences can affect following generations. Exposure to stressors before or during pregnancy is referred to as maternal adversity. Maternal adversity can engender negative and positive adaptations in brain function and behavior that can be passed along to offspring through a process termed transgenerational transmission. Specifically, maternal adversity has been associated with cognitive, neurodevelopmental and psychological effects on offspring. The temporal proximity of stressors to pregnancy and delivery may alter risk; however, an empirical understanding of the effects of stress *before pregnancy* remains limited.

There is emerging evidence to suggest that enrichment, or positive psychosocial and environmental exposures for mothers and/or their offspring, may confer protective benefits to counter adverse transgenerational transmission. Currently, epigenetics is the most prominent explanation of transgenerational transmission.[1] Epigenetics describes how interactions between the genotype and environment alters the phenotype via heritable changes in gene expression. Evidence suggests that epigenetic processes can be altered by life experiences, prenatal environmental, postnatal mother–infant interactions and juvenile social rearing with long-term consequences that affect first and second-generation offspring.[2]

In this paper, empirical findings regarding the transgenerational transmission of maternal adversity during three critical periods – childhood, pregestational adulthood and pregnancy – will be reviewed in terms of pregnancy outcomes, maternal care, offspring behavior and development, and physiological functioning. Key findings will be summarized in Table 1. Research on the transgenerational transmission of enrichment and the implications for interventions to ameliorate the consequences of adversity will also be presented. In the final section, underlying epigenetic and environmental mechanisms that have been proposed to explain how experience is transferred across generations through transgenerational transmission will be reviewed.

Early adversity

Adverse experiences that occur early in development, such as abuse during childhood, are associated with long-term consequences. For instance, young children exposed to war-related trauma exhibit lasting and severe posttraumatic stress symptoms that place them at risk for future maladaptation,[3] and childhood abuse has been found to contribute to maladaptation independent of confounding environmental and social stressors.[4] Childhood adversity is also a major risk factor for the development of mental disorders and behavioral dysfunctions, with numerous studies demonstrating that early abuse is associated with psychopathology (e.g. depression, anxiety, suicidality) and substance use in

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Table 1. *A summary of key experimental rodent models, demonstrating transgenerational transmission of early, pregestational and prenatal stress and enrichment to the next generation in terms of behavioral and physiological effects*

References	Type/timing of exposure	Behavioral outcomes for offspring	Physiological outcomes/mechanisms
Roth *et al.*[24]	1-week-old infant rats were exposed to stressed caretakers who displayed abusive behaviors	Female rats exposed to early abuse mistreated their own offspring	Early maltreatment led to changes in BDNF DNA methylation in the prefrontal cortex of adult rats and in the brains of their offspring
Franklin *et al.*[13]	Mice were exposed to chronic and unpredictable maternal separation from postnatal day 1 to 14	Early paternal stress → normally reared second and third-generation offspring displayed depressive behaviors and altered responses to novel and aversive environments	Early stress altered DNA methylation in the male germline
Leshem and Schulkin[12]	Female rats were exposed to stress as weanlings. Half (and their controls) were raised in an enriched environment post-weaning until mating. Half of the offspring in each group were raised in an enriched environment after weaning	Early maternal stress → offspring displayed increased anxiety and decreased social interaction; females showed increased fear and improved avoidance learning and males showed improved fear habituation Early maternal enrichment → offspring displayed reduced anxiety; females showed increased exploration and males showed decreased exploration and social interaction Enrichment of offspring → reduced anxiety/fear and improved avoidance learning	
Shachar-Dadon *et al.*[26]	Female rats were exposed to unpredictable stressors for 7 days and then they were either mated immediately or 2 weeks afterwards	Pregestational maternal stress (immediately prior) → all offspring displayed increased activity and anxiety and decreased social interaction; among males, shock avoidance increased and fear decreased Pregestational maternal stress (2 weeks prior) → offspring displayed reduced social interaction and in males, reduced fear; the 2-week interval mitigated effects on offspring activity and shock avoidance	
Zaidan *et al.*[27]	Female rats were exposed to chronic unpredictable stress 2 weeks before mating	Pregestational maternal stress → offspring showed abnormalities in anxiety and fear learning (e.g. unpredictable startle responses, nonlinear habituation) compared with controls	Following stress, female rats displayed increased CRF1 mRNA expression in the frontal cortex and mature oocytes. Neonatal offspring showed increased CRF1 expression at birth and experience-dependent expression in the frontal cortex and amygdala

Table 1. (*Continued*)

References	Type/timing of exposure	Behavioral outcomes for offspring	Physiological outcomes/mechanisms
Zaidan and Gaisler-Salomon[28]	Female rats underwent a 7-day unpredictable stress procedure 2 weeks before mating. Naïve offspring were mated with non-stressed rats to produce second-generation offspring	Pregestational maternal stress → second-generation offspring displayed reduced anxiety and enhanced fear learning	Stressed females and their female (but not male) offspring demonstrated elevated CORT levels; second-generation offspring from the female line showed decreased levels, whereas those from the male line showed increased levels
Lehmann *et al.*[34]	Pregnant rats were prenatally stressed. A subgroup of their offspring were postnatally stressed through repeated maternal separation	Prenatal maternal stress → offspring displayed impaired avoidance learning and enhanced pre-pulse inhibition; females showed reduced locomotor activity and males showed enhanced startle habituation Maternal separation → enhanced selective attention and improved avoidance learning; antagonized the effects of prenatal stress on pre-pulse inhibition, but prenatal stress prevented the effect of maternal separation on latent inhibition/active avoidance	
Fujioka *et al.*[35]	Pregnant rats were exposed to stress on gestational days 15 to 17	Prenatal maternal stress → offspring showed enhanced active avoidance and learning as well as decreased ambulation in the open field; foster rearing by unstressed dams attenuated effects	Offspring displayed decreased Fos (a marker of neuronal activity) expression in the amygdala
Koenig *et al.*[37]	Pregnant rats were exposed to stress during either the 2nd or 3rd week of gestation. Male offspring were tested	Prenatal maternal stress (3rd week of gestation) → male offspring displayed alterations in stress reactivity behaviors (e.g. diminished pre-pulse inhibition of acoustic startle response; disrupted sensory gating)	Adult male offspring (of females stressed during 3rd but not 2nd week of gestation) displayed prolonged elevation in plasma glucocorticoid levels following exposure to acute stress
Champagne and Meaney[33]	Lactating rats were characterized as high or low in pup-directed licking/grooming. They were then rebred and exposed to 7 days of intermittent stress during gestation. The same female rats were mated a third time without a subsequent intervention	Prenatal maternal stress → mothers who previously displayed high licking/grooming displayed low licking/grooming with their new offspring, who showed anxious and maternal behaviors in adulthood similar to low licking/grooming mothers Third mating offspring showed enduring effects of stress on both mother and offspring maternal licking/grooming	Prenatally stressed rats along with their second and third mating offspring showed reduced oxytocin receptor binding
Mueller and Bale[40]	Pregnant mice were exposed to chronic, variable stress during either the 1st, 2nd or 3rd week of gestation	Prenatal maternal stress (1st week of gestation) → male offspring displayed maladaptive stress responsivity, anhedonia and increased sensitivity to SSRI treatment	Male offspring of rats stressed during the 1st week of gestation displayed long-term alterations in central CRF and glucocorticoid receptor expression and gene methylation as well as increased HPA responsivity

			Stress early in pregnancy significantly increased expression of PPARα, IGFBP-1, HIF3α and GLUT4 in male placentas but not female placentas
Bingham *et al.*[43]	Pregnant rats were exposed to prenatal stress during the 3rd week of gestation or a daily injection of CORT. A subgroup of adult offspring were exposed to social defeat stress	Prenatal CORT injections → impaired offspring acquisition and recall of cue-conditioned fear extinction, which was further impaired by postnatal chronic stress exposure	Both prenatal stress and CORT injections decreased offspring (compared with controls) glucocorticoid receptor protein levels in the medial prefrontal cortex, hippocampus and hypothalamus as well as tyrosine hydroxylase levels in the locus coeruleus
Grundwald and Brunton[41]	Rats were exposed to repeated social stress during pregnancy. Naïve first-generation offspring and their controls were mated with control males to produce second-generation offspring	Prenatal maternal stress → second-generation male offspring displayed heightened anxious behavior; unlike controls, second-generation females did not show reduced anxious behavior at proestrus/estrus	Second females displayed enhanced ACTH and CORT responses to acute stressors, greater CRH mRNA expression in the paraventricular nucleus and reduced hippocampal glucocorticoid and mineralocorticoid receptor mRNA expression Second-generation males displayed attenuated HPA responses to acute stress and greater hippocampal glucocorticoid mRNA expression; heightened anxiety was associated with greater CRH mRNA expression in the central nucleus of the amygdala
Laviola *et al.*[51]	Pregnant rats underwent prenatal stress (gestational day 11 to 21). Offspring lived in either enriched or standard environments throughout adolescence	Prenatal maternal stress → offspring showed less affiliative/playful behavior and increased emotionality, but postnatal enrichment increased species typical and play behavior and reduced emotionality	Offspring of prenatally stressed rats displayed decreased CD4 T lymphocytes, CD8 T lymphocytes and T4/T8 ratio and increased spleen and frontal cortex levels of proinflammatory interleukin-1b (IL-1b) cytokine; they also had more marked response to cyclophosphamide-induced immunosuppression Enrichment increased anti-inflammatory IL-2 and reduced proinflammatory IL-1b production, alleviating CPA-induced immune depression; it also increased IL-1b in the hypothalamus and normalized levels in the frontal cortex
Curley *et al.*[49]	Female rats reared foster pups in either standard or communal (social enrichment) rearing conditions. Female pups from both conditions were mated as adults and reared their own offspring under standard conditions	Early maternal enrichment → increased maternal care and offspring showed reduced anxious behavior in novel environments; female offspring also exhibited higher levels of *postpartum* care when rearing their own pups, who engaged in less anxious behavior, had larger litter sizes and higher frequency of nursing	Communally reared females displayed elevated oxytocin receptor binding, and a trend for elevation was also seen in their offspring. Communally reared females and their offspring also showed decreased vasopressin receptor binding in the lateral septum

Table 1. (*Continued*)

References	Type/timing of exposure	Behavioral outcomes for offspring	Physiological outcomes/mechanisms
Cutuli *et al.*[50]	Female rats were raised in enriched or standard environments from weaning to breeding age. They were then mated and reared in standard conditions with their offspring	Early maternal enrichment → higher levels of licking, crouching and nesting maternal care behaviors; offspring showed better discriminative and spatial performance than controls	BDNF levels were increased in the frontal cortex of enriched females and the hippocampus of their offspring
Arai *et al.*[53]	Mice were exposed to 2 weeks of an enriched environment. They mated and raised offspring in a standard environment		Mice exposed to presentational enrichment and their offspring demonstrated enhanced long-term potentiation, regardless of whether offspring were exposed to enrichment
Welberg *et al.*[54]	Rats were placed in either enriched or standard environments during pregnancy and until their offspring were weaned. A group of adult offspring experienced chronic stress	Prenatal maternal enrichment → mothers displayed fewer nursing episodes while frequency of pup licking was not affected; altered offspring reactivity to acute and chronic stress	For female offspring, chronic stress increased CORT levels and reduced ACTH responses to acute stressors, but not if they had been exposed to prenatal enrichment
Maruoka *et al.*[55]	Pregnant rats were housed in either an enriched or standard environment	Prenatal maternal enrichment → female (but not male) offspring displayed decreased locomotor activity and increased time spent in the center of the open field	Maternal enrichment altered cell proliferation in the hippocampal dentate gyrus of female but not male fetuses

BDNF, brain-derived neurotrophic factor; CRF1, corticotropin-releasing factor type 1; mRNA, messenger RNA; CORT, corticosterone; HPA, hypothalamic–pituitary–adrenal axis; ACTH, adrenocorticotropic hormone; CRH, corticotropin-releasing hormone; SSRI: selective serotonin reuptake inhibitor; CPA: cyclophosphamide (an immunosuppressant agent).

adulthood.[5–8] Considering abuse and trauma survivors remain vulnerable to lasting psychological consequences, certain life events may trigger dormant symptoms. Pregnancy or the birth of a child can be particularly stressful, making it a time of increased vulnerability.[4] Women who were abused in childhood, for example, report a greater degree of suicidal ideation during their pregnancies.[9]

Studies examining the effect of early maternal adversity on pregnancy outcomes are scarce, contradictory and seriously limited by methodological challenges.[10] However, three studies have found significant associations, such that women with a history of childhood abuse had 2.6–4.8 increased odds of preterm delivery.[10] Preterm delivery, in turn, increases long-term risks for the infant, including respiratory, gastrointestinal and renal problems; cerebral palsy; visual, auditory and intellectual impairments; and other neurological disorders.[11] Although preterm delivery is not necessarily a result of transgenerational transmission, it is a noteworthy way in which maternal adversity may affect offspring.

There is also preliminary evidence that the long-term consequences of early maternal adversity affects the behavior and psychopathology of future offspring. In a study by Leshem and Schulkin, the offspring of female rats exposed to stress as weanlings exhibited increased anxiety and decreased social interactions.[12] Sex-specific effects were also observed, such that males demonstrated improved fear habituation and stress coping, whereas females demonstrated increased fear responses and agitation.[12] Another study found that mice exposed to stress from birth to 2 weeks of age displayed depressive behaviors and altered DNA methylation, both of which were transmitted across generations in a sex-specific manner such that normally reared offspring displayed similar behavioral responses and alterations in gene expression.[13] Although empirical evidence regarding the transgenerational transmission of childhood adversity remains limited, physiological alterations and epigenetic changes have been elucidated.

To begin with, childhood abuse is associated with the hyper secretion of cortisol when stressed in adulthood.[14,15] Early adversity affects future reactivity to stress by altering the developing neural circuits controlling neuroendocrine responses. Exposure to severe and chronic stress during periods of high neuronal plasticity (as in childhood) produces lasting alterations in the hypothalamic–pituitary–adrenal (HPA) axis, a major pathway in the stress response system.[16,17] It is worth noting that HPA dysregulation may explain heightened vulnerability to preterm delivery, and heightened basal cortisol in women before pregnancy has been found to be a strong predictor of preterm delivery.[14,18] Furthermore, early adversity may elevate corticotropin-releasing hormone (CRH) gene expression in the mother's brain and (during pregnancy) placenta, stimulating fetal cortisol and adrenocorticotropic hormone (ACTH) and signaling premature maturation of fetal tissue.[19,20]

As these physiological alterations are not always observed, it is possible that variations in epigenetic programming influence the long-term consequences of early adversity. Indeed, the *postmortem* hippocampal brain tissue of adults who experienced trauma or maltreatment in childhood reveal diminished glucocorticoid receptor (NR3C1 gene) expression,[21] which may explain heightened HPA responsiveness to stress.[22] Furthermore, institutionally reared children (from birth) show increased DNA methylation throughout the genome, including genes implicated in brain development, when compared with age-matched children reared by their biological parents.[23] In a rat model, early adversity produced brain-derived neurotrophic factor (BDNF) DNA methylation and reduced BDNF gene expression in the prefrontal cortex; these epigenetic alterations persisted into adulthood, were transmitted to offspring and could be 'rescued' with robust DNA methylation inhibitor treatment.[24] It is important to note that the rodents who experienced early abuse were also more likely to mistreat their own offspring. In addition to physiological dysregulation and epigenetic alterations, behavioral learning as well as psychosocial environmental continuity between the mother and her child may account for the transgenerational transmission of the consequences of childhood abuse.[25]

In sum, preliminary evidence indicates that the long-term adverse consequences of childhood abuse affect pregnancy and offspring. Women exposed to early adversity may be more susceptible to stress during a major psychosocial stressor like pregnancy. This may be due in part to HPA dysregulation along with elevated CRH and cortisol levels. Differences in gene expression as well as individual differences in the outcomes of early adversity suggest that epigenetic influences exist.

Pregestational adversity

In addition to early adversity, adverse events that occur in adolescence or adulthood, but precede pregnancy may engender transgenerational transmission. An important consideration is the temporal proximity of the adverse event to reproduction and whether its impact may wane over time. Indeed, if the parent generation is to impart useful environmental information, adversity early in life may be less relevant than adversity shortly before reproduction. Although there is limited research on the impact of pregestational stress during the different life stages of the future mother, findings indicate that adverse experiences before pregnancy can have long-term behavioral and physiological effects on offspring.

In one experimental model, female rats were exposed to stress for 7 days and either mated immediately or 2 weeks afterwards.[26] When maternal stress occurred immediately before pregnancy, offspring (compared with controls) displayed increased activity and anxiety and decreased social interaction; males also showed enhanced shock avoidance and decreased fear.[26] When maternal stress occurred 2 weeks before pregnancy, offspring exhibited enhanced social interaction, and among males reduced fear.[26] On most measures, stress immediately before mating had a greater impact than stress 2 weeks earlier, suggesting a mitigation

of the effects of adversity with the passage of time between stress and conception.[26] Compared with a previously discussed model of weanling stress,[12] both early and pregestational stress increased offspring activity in the explorative tests, reduced social interaction and improved avoidance learning in males, but only weanling stress increased avoidance learning in females. Furthermore, some of the behavioral effects of pregestational stress are similar to those of prenatal stress (discussed below), such as increased anxiety in the elevated maze, reduced social interaction and improved avoidance learning in males.[34,35,37,39] Finally, it is noteworthy that some of these behavioral effects of transgenerational transmission might be considered disadvantageous (e.g. anxiety, reduced social interaction) and others advantageous (e.g. improved avoidance learning, reduced fear) to the offspring.

Beyond behavioral effects, it is worth briefly mentioning that pregestational adversity may delay conception and affect reproductive outcomes. In experimental rat models, neonatal weight has been found to be increased in the offspring of females stressed immediately before mating,[26] although birth weight is often reduced after pregestational stress.[27] However, such findings are mixed and are not necessarily the result of transgenerational transmission. Models that explore physiological mechanisms underlying behavioral alterations provide more compelling evidence of transgenerational transmission via epigenetic mechanisms.

One study found that exposing female rats to chronic unpredictable stress 2 weeks before conception altered the emotional, learning and social behavior of future offspring.[27] Behavioral effects differed by sex, such that female offspring were more fearful, anxious, cognitively impaired and less sociable; males were also less sociable, but were less fearful and more successfully avoidant.[27] Interestingly, pregestational stress increased the expression of corticotropin-releasing factor type 1 messenger RNA (mRNA) in the ova as well as in the brains of mothers and offspring, suggesting an epigenetic route of transgenerational transmission.[27] A second study found that pregestational stress to female rats 2 weeks before mating resulted in reduced anxiety, enhanced fear learning and improved adaptive learning for second-generation offspring.[28] In addition, levels of the stress hormone corticosterone (CORT; an indicator of HPA functioning) was altered across the three generations in a sex-dependent manner.[28] Structurally, pregestational maternal adversity has been found to affect offspring by altering medial prefrontal brain morphology and increasing the number and length of dendritic spines in certain brain regions; these regional effects were shown to vary depending on the temporal proximity between adversity and conception.[29]

Many researchers maintain that transgenerational transmission is likely mediated by stress-induced epigenetic programming of future gene activity in the oocyte, whereas others contend that continuity of psychosocial environment may mostly explain the effects. Another possibility is that the long-term consequences of pregestational adversity persist into pregnancy to affect fetal development and into the *postpartum* period to alter maternal, and thereby offspring behavior. Different maternal behavior toward male and female offspring might partially explain sex differences. Compromised maternal competence is detrimental, *inter alia*, to the developing stress physiology in rat and non-human primates,[30] and its effects can persist across generations. Such effects are difficult to demonstrate in humans.

In sum, pregestational adversity to the mother may have effects on her offspring that persist into adulthood, differ by sex, differentially effect behaviors and depend on the temporal proximity of the stressful exposure to conception. Pregestational adversity to the mother can impart both resilience and impairment to offspring. Additional findings demonstrate behavioral effects on the second and third generations and elucidate physiological changes to support epigenetic routes of transmission, although further research is needed to tease apart confounding psychosocial factors. Future studies on gender differences in brain development and neural programming are also needed to better understand differential responses to maternal adversity.

Prenatal adversity

Importantly, prenatal maternal adversity (stress during pregnancy) impacts the fetal environment, and thus the fetus directly, whereas pregestational adversity does not. More research is available on maternal stress *during* rather than *before* pregnancy, and it is currently well understood that prenatal adversity can have long-term behavioral, neurobiological and psychological consequences for infants as well as mother–infant interactions *postpartum*.[31,32] Such effects of transgenerational transmission are demonstrated by experimental rat models.

To begin with, prenatal adversity has been shown to directly affect maternal behavior *postpartum*. In one study, female rats, who previously engaged in high pup-directed licking/grooming following an unstressed pregnancy, engaged in low levels of these maternal care behaviors following both a stressful pregnancy and a subsequent unstressed pregnancy.[33] The offspring showed anxious and low maternal care behaviors in adulthood, and along with their prenatally stressed mother, showed reduced oxytocin receptor binding.[33] Another study found that even brief and repeated separation of prenatally stressed pups from their dams could reverse deleterious effects on offspring avoidance learning,[34] suggesting that the effects of adversity on maternal behavior might ameliorate with the passage of time. However, it is significant to note that cross-fostering by unstressed dams has been shown to attenuate rather than completely eliminate the effects of prenatal stress on offspring,[35] and altered maternal behavior may not be necessary for transgenerational transmission. Evidence suggests that the neuroendocrine system, and thus, epigenetic processes, may be the primary mediator of prenatal effects on behavior.[32,36] Indeed, prenatal stress can predict offspring's behavior as well as their neuroendocrine stress reactivity;[31] the consequences are long-lasting, spanning from the juvenile period to adulthood.

The timing of the adverse event during pregnancy is important to consider. In one rat model, maternal stress during the 3rd, but not the 2nd, week of gestation was significantly associated with alterations in stress reactivity behaviors and prolonged elevations in glucocorticoid levels among adult male offspring.[37] Elevated maternal and fetal exposure to glucocorticoids can permanently alter HPA function in a sex-specific manner.[38] For rats, the 3rd week of gestation corresponds to a critical period during which time the fetal HPA axis begins to release its own ACTH and CORT.[39] However, the male offspring of mice exposed to stress earlier in gestation (1st week) have also been found to display maladaptive stress reactivity and depressive behaviors, accompanied by long-term differences in central corticotropin-releasing factor (CRF) and glucocorticoid receptor expression as well as increased HPA reactivity.[40] In addition, early prenatal stress increased the expression of particular genes in male but not female placentas, suggesting that differences in placental epigenetic mechanisms may explain sex-specific transgenerational transmission.[40]

Many behavioral findings are sex specific, such that male offspring are often more vulnerable prenatally. In a study on rats, stress during pregnancy altered HPA regulation in the mother, her offspring and the second generation in a sex-dependent way; second-generation females demonstrated greater stress responses, whereas second-generation males demonstrated attenuated stress responses and heightened anxious behavior.[41] Heightened anxiety was associated with greater CRH mRNA gene expression in the amygdala, and attenuated stress responses were associated with greater glucocorticoid mRNA expression in the hippocampus and impaired feedback to the HPA.[41] Prenatal exposure to adverse events has been found to impact HPA and glucocorticoid receptor activation in the placenta and diverse regions of the brain.[42] In one study, the offspring of rats exposed to either a daily injection of CORT or prenatal stress during the 3rd week of gestation all displayed decreased glucocorticoid receptor protein levels in the medial prefrontal cortex, hippocampus and hypothalamus, as compared with controls.[43]

In humans, elevated levels of depression during the third trimester of pregnancy has been associated with increased DNA methylation of the glucocorticoid receptor gene (NR3C1) in newborns (but not mothers), which predicted cortisol and HPA stress reactivity at 3 months of age.[44] Elevated levels of NR3C1 DNA methylation have also been found in the children of women who experienced intimate partner violence during pregnancy.[45] In addition, prenatal adversity is associated with excess amounts of CRH and cortisol, impaired fetal habituation to stimuli, and temperamental difficulties in infants.[16] Perceived maternal stress during pregnancy can predict infant cortisol reactivity during neonatal and postnatal assessments, and neonatal cortisol reactivity predicts behavioral reactivity at 10 months of age.[46] Similarly, exposure to elevated concentrations of maternal cortisol during the second and third trimesters predicts larger infant cortisol responses to and prolonged behavioral recovery from a blood draw.[47] In contrast, mothers with posttraumatic stress disorder (PTSD) who experienced trauma during pregnancy and their children had lower (rather than higher) cortisol levels.[48]

In sum, prenatal adversity has been found to affect both maternal and offspring behavior. Transgenerational transmission may be mediated primarily through epigenetic processes, as there is a growing evidence base for an association between prenatal maternal stress and altered gene expression in offspring. Epigenetic pathways appear to operate via the neuroendocrine system, as glucocorticoid, cortisol and CRH levels have been found to be affected by prenatal stress. In turn, the HPA system plays a significant role in fetal programming and can lead to long-term consequences. Finally, models of prenatal stress have identified sex-specific and temporal-specific effects on offspring behavior, such as stress responses, that warrant further exploration.

Transgenerational enrichment

Enrichment refers to positive psychosocial and environmental exposures. In rodent modes, enrichment often involves the addition of a running wheel, tube or ladder to the environment or more opportunities for social interaction, which are believed to increase cognitive and/or motor stimulation. Maternal and/or offspring enrichment may confer positive benefits and protect against or ameliorate the negative effects of transgenerational transmission.

Early maternal enrichment has been found to have a positive impact on *postpartum* care and offspring behavior. In one study, female rats who were reared in socially enriched, communal conditions by foster mothers later showed improved maternal care when rearing their own offspring in standard conditions.[49] The offspring of rats raised in enrichment conditions exhibited reduced anxious behaviors, and female offspring displayed higher levels of maternal care when rearing their own pups, who also displayed less anxious behaviors.[49] Elevated oxytocin receptor binding and decreased vasopressin receptor binding was observed in both enriched mothers and their offspring.[49] Another study found similar effects, such that female rats raised in an enriched environment from weaning until breeding age demonstrated higher levels of maternal care behavior.[50] This route of transgenerational transmission was linked to BDNF-induced neuroplasticity, such that the behavior of enriched females and their offspring was associated with profound rearrangements in neurotrophin pattern, and higher BDNF levels were expressed in the frontal cortex of enriched mothers and in the hippocampus of their offspring.[50]

In a previously discussed study by Leshem and Schulkin, female rats exposed to stress as weanlings were either raised in enriched or standard environment post-weaning until mating.[12] Early maternal stress followed by subsequent pregestational enrichment had an anxiolytic effect on offspring, reducing anxious behaviors (elevated following early stress without enrichment).[12] Pregestational enrichment prevented impairment of startle habituation in female offspring, and effects on social interaction were most marked in male offspring,

https://doi.org/10.1017/S2040174416000416 Published online by Cambridge University Press

suggesting that social behavior may be more vulnerable to transgenerational transmission among males.[12] Offspring who were then raised in an enriched environment post-weaning exhibited reduced anxiety in the open field on all measures of explorative behavior.[12] On other tests, the effects of offspring enrichment differed by sex: males (but not females) in the elevated maze demonstrated reduced anxiety as well as increased habituation to startle and improved avoidance learning.[12]

Similarly, when offspring of prenatally stressed rats were exposed to postnatal enrichment, negative behavioral effects were reversed in that offspring demonstrated greater play behavior and less emotionality.[51] Beyond environmental enrichment, there is evidence to suggest that postnatal drug treatment (pharmacological enrichment) can alleviate offspring impairment following prenatal stress.[52] Importantly, mice exposed to 2 weeks of pregestational maternal enrichment along with their offspring have both been found to have enhanced long-term potentiation (LTP), regardless of whether offspring were or were not exposed to postnatal enrichment,[53] supporting the existence of transgenerational transmission of maternal experience before pregnancy.

Prenatal enrichment has also demonstrated effects on maternal care and offspring behavior. Rats who were exposed to an enriched environment during pregnancy and until their offspring were weaned displayed higher levels of maternal care behaviors and their offspring exhibited altered reactivity to both chronic and acute stress.[54] Female offspring exposed to chronic stress in adulthood had increased CORT levels and reduced ACTH responses to acute stressors, but only if they had not been exposed to enrichment (controls).[54] Thus, the prenatal and postnatal enrichment selectively altered HPA programming. In another study with sex-specific results, prenatal maternal enrichment resulted in behavioral differences among female offspring and influenced cell proliferation in the hippocampus of female (but not male) fetuses.[55]

In sum, pregestational and prenatal maternal enrichment has been found to improve maternal care and ameliorate the transgenerational consequences of adversity on offspring in a sex-specific manner. Postnatal enrichment can also be remedial for offspring, annulling the effects of pregestational stress, depending on the test and sex. Although more research is needed, the effects of enrichment appear to be primarily anxiolytic, reducing anxiety and fear and promoting explorative and social behavior. If potential damage to progeny and its prevention can both occur in the parent generation, remedial pregestational, prenatal, and postnatal enrichment could be combined to protect the offspring generation from the transgenerational transmission of adversity. As animal models are limited in their ability to assess complex psychosocial enrichment, human studies are needed, as the consequences of adversity might be ameliorated through therapeutic interventions to promote resilience. The transgenerational transmission of enrichment could have broad implications that warrant further investigation.

Mechanisms of transgenerational transmission

Epigenetic and environmental mechanisms have been proposed to explain how experience is transferred across generations through transgenerational transmission. In the preceding sections, hormonal and neural changes associated with adversity and enrichment at different stages were discussed. These changes are thought to be epigenetic in nature. Epigenetic programming is a prominent explanatory mechanism of transgenerational transmission that will be discussed further in this section, along with explanatory environmental mechanisms that involve fetal development, nurturing and contextual stressors.

To begin with, transgenerational transmission cannot simply be attributed to evolution, culture and/or genetic transmission alone. From an evolutionary perspective, transgenerational transmission ensures that the next generation is better prepared for an adverse environment. However, it remains unclear how adverse outcomes, such as transgenerational transmission of PTSD or schizophrenia,[56,57] could represent adaptive effects. In light of evidence that environmental adversity (e.g. traumatic experiences) can become encoded with brain and behavior consequences for the next generation, recent human research links dysfunctional outcomes with epigenetics.[1,58] Epigenetics refers to interactions between the genotype and the environment that alter the phenotype via heritable changes in gene expression without underlying change in DNA sequence. Key mechanisms involved in epigenetic gene regulation include DNA methylation (silencing or enhancing gene expression) and histone modifications, which alter the functional qualities of the DNA sequence. Evidence suggests that epigenetic processes can be affected by life experiences, prenatal environmental, postnatal mother–infant interactions and juvenile social rearing with long-term consequences that effect first and second-generation offspring in a differential, sex-specific manner.[2]

As previously discussed, maternal stress before or during pregnancy results in elevated cortisol levels in both the mother and the fetus, and the activation of cortisol or CORT impacts the expression of information molecules (e.g. CRH) as well as neurotransmitter and glucocorticoid receptor sites. Chronic and prolonged exposure to stress hormones may explain the effects of transgenerational transmission on pregnancy and offspring, and epigenetic changes in chromatin is proposed to underlie the transgenerational programming effects of maternal stress via alterations in glucocorticoid signaling.[59] Experimentally increasing prenatal exposure to glucocorticoids results in reduced birth weight and increased likelihood of developing disorders related to cardiovascular function, glucose homeostasis, HPA activity and anxiety-related behaviors in adulthood.[42,59] In humans, it is also associated with lower birth weight and higher blood pressure in offspring.[59] Interestingly, glucocorticoid facilitation of CRH gene expression can elicit avoidance behaviors through epigenetic mechanisms, such as histone modifications (e.g. deacetylation). Such long-term changes in CRH expression may explain transmission.

Epigenetic regulation of CRH and other information molecules has been detected in placental tissue.[60,61] Considering CRH and glucocorticoids are implicated in an arousal pathway involving exaggerated anticipation of negative events, it follows that the upward regulation of CRH in the placenta is linked with the pathogenesis of chronic anxiety, fear and heightened vigilance in offspring.[60] In addition, CRH facilitates parturition and conditions of duress can cause glucocorticoids to prematurely elevate CRH levels in the placenta, increasing vulnerability to preterm delivery.[62,63] Preterm birth may serve to 'rescue' the fetus from an adverse environment or reduce the allocation of resources to a pregnancy occurring during stressful circumstances.[64,65] It is important to note that higher levels of CRH during pregnancy also increases maternal vulnerability to a suppressed HPA axis after delivery and *postpartum* depression, for which the CRH-R1 receptor has been implicated.[66–68] Changes in maternal and offspring HPA function, which can be altered via stress-induced changes to CRF (or CRH) expression,[27] are often accompanied by behavioral effects. One key feature impacting these outcomes is social contact. Early social experiences affect neural systems, including CRH and glucocorticoid receptors, as well as brain morphology,[29,69] and cross-fostering experiments show that changes in demethylation are linked to the transmission of social behaviors as well as CRH expression.[70] Together, CRH and social factors can impact behavior and brain function.

Parental responsiveness has profound effects on HPA as well as extra-hypothalamic CRH expression. Nurturing maternal behaviors (e.g. grooming) can buffer offspring from the over activation of HPA when they are later exposed to adversity in adulthood.[71] Furthermore, studies with monkeys show that rearing conditions have long-term implications for neuropeptides, steroids, neurotransmitter expression and behavior.[72] Maternal deprivation in macaques results in elevated levels of cortisol and CRH, whereas macaques in normal maternal-reared conditions develop elevated levels of oxytocin and lower levels of CRH.[73,74] In addition, macaques with the anxiety risk allele of the SLC6A4 gene, who were reared under conditions of maternal separation, were subsequently found to have increased DNA methylation of the gene.[75] Evidence that maternal care can alter the expression of behavioral and endocrinal stress response genes (as well as hippocampal synaptic development) supports an epigenetic route for transgenerational transmission of stress reactivity.[76] For instance, impaired maternal care in mice causes female offspring to exhibit increased fear of novel objects and decreased exploratory behavior.[77] Additional animal research has shown that maternal care influences the subsequent maternal behavior of female offspring, a self-perpetuating cycle of nurturing competence that may be partially explained by epigenetic effects (e.g. oxytocin receptor gene expression).[78,79]

Paternal care also plays an important role in the functional development of the brain. Father-deprived animals display dysfunctions in anxiety-related subcircuits, including CRH-expressing neurons in the medial bed nucleus of the stria terminalis (BNST), prefrontal and limbic regions.[80–82] In light of such effects, the transgenerational transmission of paternal experience is receiving increasing attention.[13] It has been proposed that stress to the father affects biological and behavioral phenotypes, causing epigenetic modification of DNA that is expressed in germ cells and thus, transmitted to offspring.[83,84] In one study, the offspring of male mice exposed to social stress displayed more depressive and anxious behaviors as well as differences in levels of plasma CORT and vascular endothelial growth factor.[84] Furthermore, the father's nutritional diet, toxicological exposures (e.g. alcohol, nicotine, cocaine), age and phenotypic variation can lead to alterations in offspring development that are suggestive of an epigenetic germline route of paternal transmission.[85,86] Alternatively, or in combination with paternal transmission, life experiences may lead to changes in mate quality and preference, which can subsequently influence maternal investment.[86]

There is ample evidence to support the transmission of adaptations to environmental circumstances. In animal studies, for instance, experimentally improved LTP is transmitted to improve offspring LTP,[53] and mothers exposed to predation threat before reproduction transfer protective behaviors to their offspring.[87,88] In addition, human observational studies suggest that phenotypic variation acquired from the parental generation's environment can be transmitted.[89] Studies on the Dutch famine of 1944 indicate that poor maternal nutrition during pregnancy is associated with low birth weight as well as a greater risk of metabolic and cardiovascular disease in offspring.[90] The grandchildren of women who were undernourished during pregnancy also displayed increased neonatal adiposity,[91] a potentially protective adaptation to uncertain food supply. Furthermore, severe changes in the paternal grandmothers' food availability (before puberty) is associated with their granddaughters' cardiovascular mortality risk.[92] While paternal grandmothers' food supply during the slow growth period (SGP; mid-childhood) is associated with the mortality risk of granddaughters, paternal grandfathers' food supply during the SGP is associated with the mortality risk of grandsons.[93] This time- and sex-specific influence of ancestral nutrition during the SGP has been replicated[94] and may be mediated by sex chromosomes.[89]

On a related note, maternal stress can influence fetal programming of obesity and metabolic disease.[95,96] For instance, pregestational exposure to famine is associated with decreased DNA methylation of insulin-like growth factor 2 (IGF2), which affects growth and development,[97] and increased methylation of interleukin 10 and leptin,[98] both of which are obesity-related candidate genes. Neonatal epigenetic gene promoter methylation has also been associated with adiposity during childhood,[99] maternal obesity increases proinflammatory cytokines that can cause peripheral and intrauterine inflammation as well as offspring brain inflammation, whereas maternal diabetes can lead to hyperglycemia, inducing chronic intrauterine fetal tissue hypoxia and oxidative stress.[100] The combination of maternal pregestational (and/or gestational) diabetes and obesity has been

associated with an increased risk of autism spectrum disorder and co-occurring intellectual disability in offspring.[100] These findings support the metabolic imprinting theory that intrauterine exposures have 'fetal programming' effects that can permanently alter offspring metabolic patterns and long-term risk for disease.[101]

The intrauterine period has been implicated as the most sensitive time for the establishment of epigenetic variability, which in turn affects offspring development, cell- and tissue-specific gene expression and risk for a range of disorders.[96] For instance, epigenetic alterations may mediate the effects of prenatal and postnatal exposures on the development of food allergies and other allergic diseases, which develop through complex environmental and genetic interactions.[102–104] The *in utero* environment is regulated by the placenta, which is highly susceptible to maternal distress, and altered gene expression within the placenta has been associated with adverse birth outcomes.[32] Increased expression of IGF2 and decreased expression of IGF1 in the placenta, for example, is associated with greater risk of intrauterine growth retardation.[105] In addition to epigenetic routes of transgenerational transmission, maternal–placental–fetal endocrine factors and maternal nutrition during pregnancy can exert programming effects via fetal telomere length.[106] A recent study also found that maternal stress during pregnancy altered vaginal microflora and bacterial exposure (e.g. swallowed) during birth, affecting neonatal gastrointestinal microbiota and brain amino acid composition.[107]

In sum, there are many forms of fetal programming. *In utero* environment as well as fetal exposure to the physiological consequences of maternal stress can impact offspring neurotransmitter and neuropeptide expression, increasing the long-term risk for negative health and behavioral outcomes. Pregestational and prenatal conditions can also affect fetal brain development, impacting cognitive and affective functioning as well as the size of limbic and frontal brain regions.[106] Many effects of transgenerational transmission appear to occur independently from changes in the genomic DNA sequence, and there is evidence for the prominent role of epigenetic mechanisms. Of course, the other side of evolution is endless adaptation and expansion to limit adverse effects of transgenerational transmission.

Conclusion

Concern for the infant's future underlies much of the research on transgenerational transmission. The developmental perspective that early experience is formative of long-term behavioral and cognitive patterns is reflected in the numerous studies that have demonstrated affects of adversity during the prenatal, perinatal and postnatal periods on offspring brain development, stress reactivity and behavior regulation. However, developmental logic has been applied to an even earlier time – before pregnancy – far less often. Currently, our empirical understanding of the link between stress before conception and its remote outcomes on progeny remains limited. This is especially relevant now, as nongenomic and epigenetic transmission offer a conceptualization of how experience may be transferred across generations without enculturation.

Going forward, a unifying view of stress vulnerability and resilience proposes connecting genetic predisposition and programming sensitivity to contexts of experience–expectancy and transgenerational epigenetic traits.[29] Cross-fostering experiments in particular will be critical to determine whether stress before conception primarily exerts its effects on offspring through behavioral and/or epigenetic mechanisms of transmission. Future research should also address the adaptive and maladaptive nature of transmissions as well as the extent of individual, familial and societal consequences. A knowledge base for remedial interventions is also necessary to focus on educational and therapeutic strategies and stem the escalation of risk across generations.

Acknowledgments

None.

Financial Support

This research received no specific grant from any funding agency, commercial or not-for-profit sectors.

Conflicts of Interest

None.

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