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Maternal Allostatic Load as a Predictor of Adverse Pregnancy Outcomes and Offspring Development in the F3 Generation: Evidence from a Rat Model of Transgenerational and Multigenerational Stress

Teddi A. Reynolds[1], Mirela Ambeskovic[1], Erin A. Falkenberg[1], Oluwagbohunmi A. Awosoga[2], and Gerlinde A.S. Metz[1,3*]

Abstract

Clinical studies suggest that cumulative maternal stress and high allostatic load are associated with higher risk of developmental and psychophysiological disorders in the offspring. Here, we adopted the clinical concept of allostatic load to a rat model of trans- and multigenerational stress. We developed an index of maternal allostatic load as a predictive tool for adverse pregnancy and offspring health outcomes. The new maternal stress index (MSI) was used to quantify sex-specific cumulative impacts of ancestral stress across four generations. F2 mothers born to a lineage of maternal transgenerational prenatal stress (TPS) or multigenerational prenatal stress (MPS) and their F3 offspring underwent physiological and behavioural assessments. Ancestral stress altered pregnancy outcomes, with higher fetal resorption following TPS and slower pregnancy weight gain following MPS. Male and female F3 TPS offspring showed impaired sensorimotor development at postnatal day (P) 9, while only males displayed increased anxiety-like behaviours at P15. Adult F3 TPS and MPS females showed heightened behavioural and physiological stress responses. Moreover, ancestral stress altered mineral deposition in hair, reflecting dysregulated Na/K metabolism. The TPS lineage displayed the largest impact of stress with age-specific sex differences. High MSI scores served as robust indicators of maternal corticosterone, glucose and gestational weight gain. MSI scores also predicted anxiety-like behaviours in adult male but not female offspring. Thus, the MSI may provide a useful indicator of the cumulative physiological burden of maternal stress. Tools like the MSI may facilitate knowledge translation from preclinical models to human populations and back.

Keywords: Prenatal stress; Allostatic load index; Match/mismatch hypothesis; Developmental origins; Maternal health; Offspring development; Sex differences; Anxiety-like behaviour; Hair mineral analysis; Metabolism; Glucose; Corticosterone.

Introduction

Gestation is a period of particular vulnerability to stress and other adverse experiences for both the mother and her unborn offspring [1-4]. Prolonged gestational stress has been recognized as a prime risk factor for adverse pregnancy outcomes, such as preterm birth [5]. Moreover, maternal stress can also affect hypothalamic-pituitary-adrenal (HPA) axis function of the fetus, thus raising the risk of metabolic disorder, such as diabetes, and cardiovascular disease in the offspring's later life [6-8]. Programming

Affiliation:
[1]Canadian Centre for Behavioural Neuroscience, Department of Neuroscience, University of Lethbridge, Lethbridge, Alberta T1K 3M4, Canada

[2]Faculty of Health Sciences, University of Lethbridge, Lethbridge, Alberta T1K 3M4, Canada

[3]Southern Alberta Genome Sciences Centre, University of Lethbridge, Lethbridge, Alberta T1K 3M4, Canada

***Corresponding author:**
Gerlinde A. Metz, PhD, Canadian Centre for Behavioural Neuroscience, Department of Neuroscience, University of Lethbridge, 4401 University Drive, Lethbridge, Alberta, Canada

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of the fetal stress response by maternal stress may also alter the brain's developmental trajectory and heighten the risk of bipolar disorder, anxiety disorders, depression, impairments in intellect and language development, autism and schizophrenia [9-12]. The consequences of prenatal stress also propagate to subsequent generations via heritable epigenetic mechanisms [13, 14] and may contribute to adverse reproductive and birth outcomes, as well as mental and metabolic disorders in the unexposed offspring [5, 15-19]. Moreover, prenatal stress occurring repeatedly across several subsequent generations may promote new behavioural traits [20] and sex-specific stress resilience [21] in spite of a vulnerability to anxiety-like behaviours [22, 23]. The finding that trans- and multigenerational stress may evoke adaptive responses support the match/mismatch hypothesis stating that individuals fare better when adaptation to prenatal or early postnatal experiences, such as stress, is met with similar lifetime experiences [24-27]. The theoretical construct of allostatic load (AL) has been developed to estimate the impact of cumulative lifetime stresses on health in mothers and their children [28]. AL refers to prolonged or repetitive stress that challenges allostasis and the adaptive capacity of the autonomic nervous system and HPA axis, thus inducing cumulative damage to the body [28]. AL indices provide a theoretical basis for understanding the complex and multi-layered biological mechanisms of the impact of chronic and toxic stress on health outcomes [29]. The combination of assessments of multiple biological systems and endocrine variables provides a particularly robust predictor of adverse health outcomes as opposed to any single marker. High AL has been recognized as a primary cause of adverse pregnancy outcomes, inflammation and other adverse health conditions [30]. While AL has become the most popular clinical framework for risk prediction, the use of animal models is vital to understand the mechanistic aspects of stress programming. The recent development of the rat cumulative AL measure (rCALM) became the first AL-based assessment tool for rodent models [31]. The rCALM provides an effective translational assessment of cumulative lifetime stress burden and the therapeutic effectiveness of interventions [31].

While maternal distress during pregnancy may be causally related to adverse offspring health [32, 33], a tool for the objective and comprehensive assessment of gestational stress in an animal model is still lacking. To extend previous research, we propose a new maternal stress index (MSI) in rats as a translational AL measure based on markers that are assessed in human pregnancy. In this proof-of-concept study, we validated individual maternal biomarkers and the MSI using two rat models of chronic generational stress, to demonstrate their predictive power of adverse pregnancy and offspring developmental outcomes. The two models of stress included transgenerational prenatal stress (TPS) and multigenerational prenatal stress (MPS), which both produce characteristic changes in maternal and offspring behaviour and physiology in the F2 and F3 generations [16, 18-20, 22, 23, 31]. The TPS lineage experienced gestational stress within the first generation, followed by non-stressed pregnancies afterwards. The MPS lineage experienced gestational stress in each generation. Moreover, the present study investigated age-dependent sex differences in response to maternal TPS and MPS in the young and adult F3 generation. The findings suggest that a composite index such as the MSI provides a robust assessment of stress-associated health risks. Tools such as the MSI may facilitate knowledge translation from experimental to clinical studies and reverse.

Method

Animals and experimental design

This research involved 15 pregnant female Long-Evans hooded rats of the filial 2 (F2) generation and their filial 3 (F3) male and female offspring (n=188; Control=60, TPS=54, MPS=74) born to three lineages raised under closely controlled housing and testing conditions. A local breeding colony was used to generate (1) a transgenerational prenatal stress (TPS) lineage, in which only the F0 parental generation was stressed during pregnancy; (2) a multigenerational prenatal stress (MPS) lineage in which each parental generation (F0, F1, F2) was stressed during pregnancy; and (3) a non-stressed Control lineage consisting of naïve, handled animals that were not experimentally stressed (Figure 1A; [19]). In each generation nine naïve males were bred with 23-37 stressed or naïve females to generate the F1, F2 and F3 generations, respectively (Figure 1A). The JAX Colony Management System (JCMS; Jackson Laboratory, Bar Harbour, ME, USA) was used for pedigree tracking [34]. Males were paired with females for 1 hr/day to allow for timed pregnancy. The exact timing of gestational length, prepartum and postpartum maternal behaviour were determined using an infrared security system (CCTV Cameras, Panasonic, and Newark, NJ, USA) [18, 19]. Gestational stress was induced daily during gestational days (G) 12-18 using a semi-random sequence of morning or afternoon 20-min restraint and 5-min swim in room-temperature water (Figure 1A; [19, 22]). Bystander effects of stress were avoided by using designated testing and housing spaces. A maximum of three offspring per litter of each sex were randomly selected for behavioural phenotyping in the F3 generation. Offspring were tested from postnatal day 9 (P9) into adulthood as outlined below (Figure 1C). All housing, handling, testing and tissue sampling conditions were kept consistent across generations. All rats and their ancestry were raised at the University of Lethbridge local vivarium and housed in standard polycarbonate shoebox cages (45.5 x 25.5 x 20 cm) on corn cob bedding. The light cycle was 12:12 h with lights on at 7:30 am. All procedures

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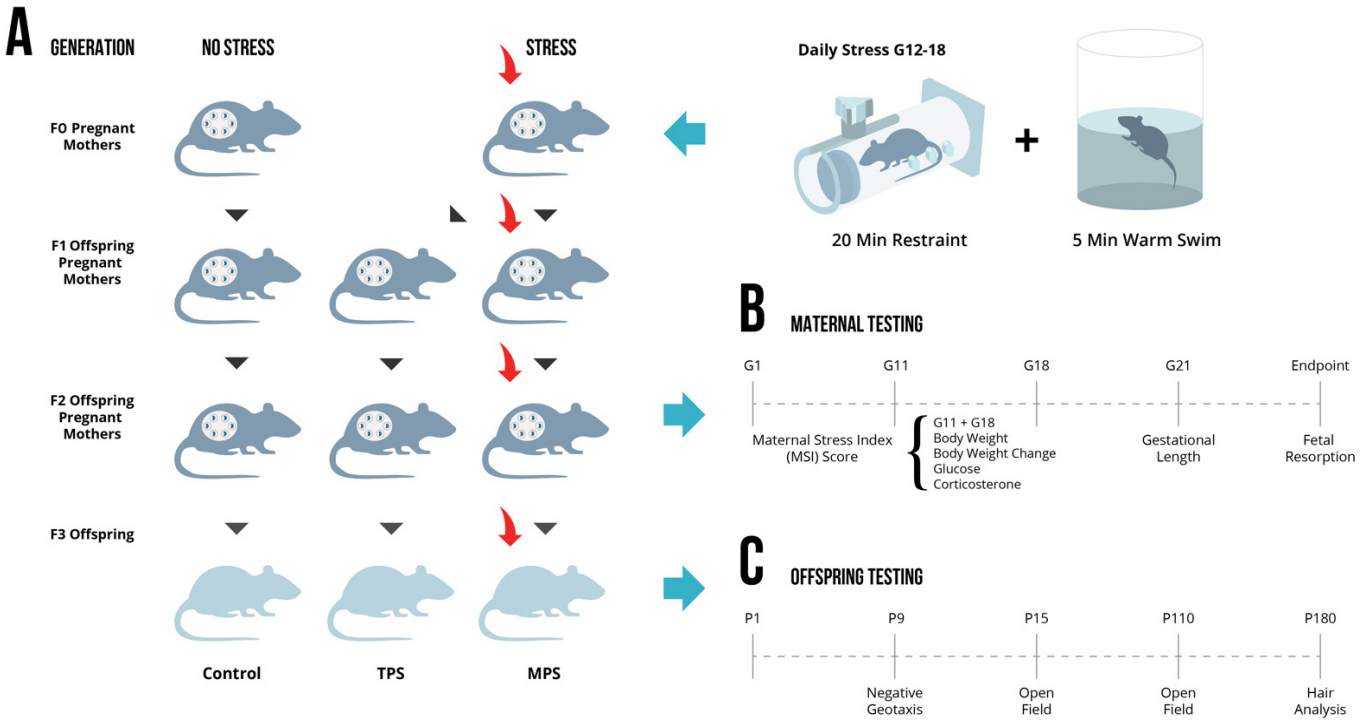
in this study were approved by the University of Lethbridge Animal Care Committee in compliance with the standards set forth by the Canadian Council for Animal Care.

A) Pregnant dams were stressed G12 to G18 with daily 5 min swim and 20 min restraint to generate ancestral stress lineage or left undisturbed to generate non-stressed lineage. Ancestral stress lineage was generated by stressing (red arrows) pregnant dams over three consecutive generations (F0, F1, F2) to produce F3 multigenerational stress (MPS) or only in first generation (F0) to produce transgenerational stress (TPS) offspring. This experiment used F2 generation pregnant mothers and their F3 generation Control, MPS and TPS offspring. (B) F2 mothers were assessed across pregnancy G11 and G18 for body weight, glucose, and corticosterone markers. Gestational length and fetal reabsorptions were also documented. (C) F3 male and female offspring were assessed for developmental trajectories longitudinally at P9, P15, P110, and P180 in negative geotaxis, open field and hair mineral analysis, accordingly.

Antepartum analysis of maternal parameters

Maternal weight was recorded after mating activity was observed. Pregnancy was confirmed by a weight increase of approximately 30g by G11 and it was determined if the pregnant dam required assignment to a stress regimen. The baseline pregnancy weight was recorded on G1, and weight gain was continuously monitored throughout G11, G18 and G21 (Figure 2A). Blood samples (0.6 ml) were also collected prior to pregnancy, on G11, and G18 (Figure 1B) from the tail vein while under isoflurane anaesthesia. First, the blood samples were used to measure glucose using an Ascensia Breeze Blood Glucose Meter (Bayer, Toronto, ON, Canada) with test strips. The remaining blood was used to determine corticosterone (CORT) levels using an enzyme-linked immunosorbent assay (ELISA) commercial kits (Cayman Chemical, Ann Arbor, MI, USA). The time of delivery was recorded and used to calculate the gestation length in hours [19].

Figure 1: Ancestral stress paradigm and maternal and offspring testing timelines.



A) Pregnant dams were stressed G12 to G18 with daily 5 min swim and 20 min restraint to generate ancestral stress lineage or left undisturbed to generate non-stressed lineage. Ancestral stress lineage was generated by stressing (red arrows) pregnant dams over three consecutive generations (F0, F1, F2) to produce F3 multigenerational stress (MPS) or only in first generation (F0) to produce transgenerational stress (TPS) offspring. This experiment used F2 generation pregnant mothers and their F3 generation Control, MPS and TPS offspring. (B) F2 mothers were assessed across pregnancy G11 and G18 for body weight, glucose, and corticosterone markers. Gestational length and fetal reabsorptions were also documented. (C) F3 male and female offspring were assessed for developmental trajectories longitudinally at P9, P15, P110, and P180 in negative geotaxis, open field and hair mineral analysis, accordingly.

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Postpartum analysis of pregnancy outcomes

Litter sizes were recorded at parturition, and each pups' sex was determined measuring anogenital distance. Special note was taken of stillbirths. The health of the litters was checked and counted daily to determine any missing pups. Following pup weaning approximately at postnatal day 21-22 the dams were euthanized and their uterine horn was collected in order to determine the number of implantation sites. The difference between the initial implantation sites and the resulting litter size was calculated to determine the number of pups that we resorbed during gestation. These results are presented as resorption rate.

Maternal stress index (MSI) calculation

The MSI was calculated throughout gestation by comparing the individual data points to the control group distribution at each timepoint [G1 (baseline), G11, G18, and G21] using calculated z scores, which were then converted into a percentile. Markers included maternal total weight and weight change, where a marker in the 25th percentile was considered dysregulated and given a score of 1, as well as glucose and corticosterone, where the 75th percentile was considered dysregulated. A hard cut-off was used here as the distributions for these metrics (measurements) were normal. If a marker was within a healthy range, the animal was given a score of 0 for that marker. The individual scores were added up to get a number between 0 and 4 for each animal at each time period, with a score of 0 denoting the lowest amount of dysregulation due to stress and a score of 4 showing the highest amount of dysregulation.

Behavioural analyses

Negative Geotaxis. The negative geotaxis task (Figure 3A) was used to monitor early sensorimotor development of the offspring [19, 35]. On P9 pups were placed face down on a plastic mesh sheet maintained at a 40° angle. The time it took for the pup to turn around 180° from a downward facing angle to an upward facing angle was recorded. In addition, the total time facing up and the number of falls off the apparatus were recorded [36].

Exploratory Motor Activity in an Open Field. On P15 offspring was placed individually in the centre of an open field apparatus (Figure 3C) black Plexiglas, 42cm x 42cm, with 9 fields to measure horizontal exploratory activity and anxiety-like behaviour. The behaviour was video recorded for an interval of 5 min. The video recordings were analyzed for the number of centre vs. wall fields entered.

In adult offspring on P110, exploratory open field activity was recorded using an automated open field apparatus (Figure 4A; AccuScan Instruments Inc., OH, USA). Rats were placed individually into transparent Plexiglas boxes for a period of 10 minutes. Infrared sensors connected to a computer recorded the animal's horizontal and vertical exploratory movements as indicators of anxiety-like behaviours in the open field. The time in centre square, total distance travelled, and total number of vertical movements (rearing) were recorded [22].

Hair trace element analysis

Hair was collected upon perfusion at P180 with stainless steel scissors and stored in a plastic bag. Hair mineral analysis was performed by CanAlt Health Laboratories (Concord, ON, Canada), to determine the levels of K and Na. Here we calculated and reported Na/K ratio, which has been shown to predict adrenal activity and related health outcomes, in particular function of stress response system and the risk for hypertension [37, 38]. For the hair analysis, 300 mg of finely cut hair was transferred into centrifuge tubes. To each sample 3.0 ml of nitric acid (HNO_3) was added. After an incubation period of 25 minutes, samples were subjected to acid microwave digest to stabilize the elements. The solution was analyzed by inductively coupled plasma mass spectrometry (ICPMS). Sample results were quantified by comparison with calibration solutions of known concentrations [37].

Statistical analysis

Statistical analysis was performed using SPSS 20 for Windows 11.5.0 (IBM Corporation, Armonk, NY, USA). After confirming that the data were normally distributed by a Shapiro-Wilk test, an ANOVA was used. A mixed measure ANOVA was performed for the maternal MSI, and a two-way ANOVA was performed for the offspring health with Treatment and Sex as the independent variables and the behavioural health outcome as the dependent variable. In case outliers were revealed, the data were winsorized, and in the case of a breach in the assumption of normality necessary for an analysis of variance, the appropriate transformation was used. In every case where significance was found a Tukey post-hoc analysis was performed to specify the change. All results are shown as the means ± standard error of the mean (±SEM).

Results

Ancestral stress altered gestational weight gain and uterine receptivity

A mixed measures ANOVA was performed to determine the effect of stress on maternal weight gain during pregnancy among F2 dams (n=5 Control, n=4 TPS, n=6 MPS). There was no significant effect of Time or Treatment, but there was a significant interaction of Time x Treatment ($F(4,66)=7.83$, $p<0.001$, $\eta^2=0.32$; Figure 2A). A pairwise comparison revealed slower weight gain in MPS dams starting at G18; the total weight gain during pregnancy in Control dams was 98.9g, 99.9g in TPS dams and only 81g in MPS dams.

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However, a one-way ANOVA showed no effects of prenatal stress and ancestral stress on the gestation length in F2 dams ($F(2,32)=1.30$, $p=0.29$, $\eta^2=0.08$; Figure 2B).

Furthermore, a one-way ANOVA was performed in order to evaluate the effect of stress on offspring birth outcomes (n=5 Control, n=4 TPS, n=6 MPS). Inspection of uterine tissues revealed resorption of fetuses during pregnancy across all groups (Figure 2C). TPS mothers resorbed more of their offspring than Control and MPS animals ($F(2, 30)=3.35$, $p<0.05$, $\eta^2=0.18$; Figure 2C). Nevertheless, litter size was not significantly changed by generational stress, with Control animals having an average of 11.8 pups, TPS dams 12.2 pups and MPS dams 12.8 pups.

A) Maternal weight change during gestation altered by TPS and MPS treatment. B) Gestation length in F2 Control, TPS and MPS dams. C) Resorption rates in F2 Control, TPS, and MPS dams. Error bars show SEM. Asterisk * denotes a significant difference at $p<0.05$.

Ancestral stress altered offspring developmental trajectories

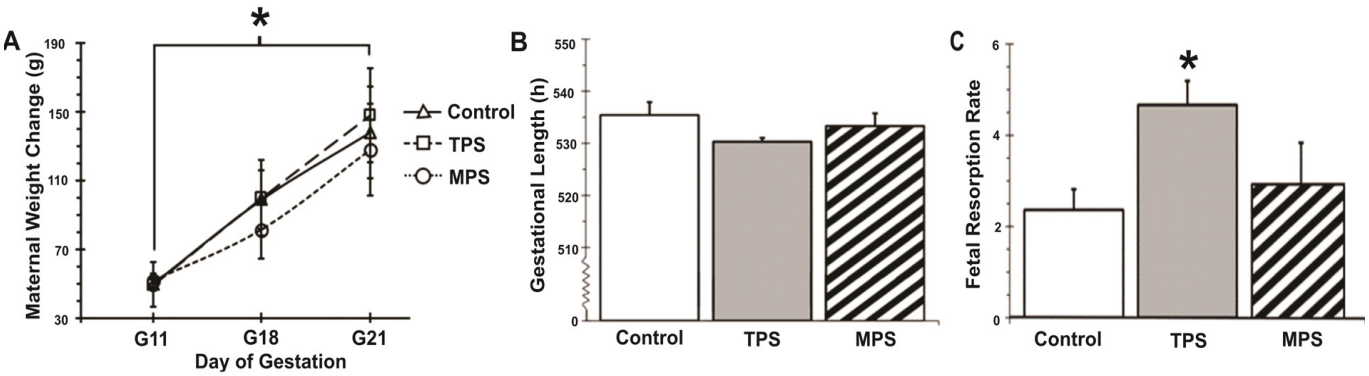
Early development of motor and vestibular functions in negative geotaxis (Figure 3A) were assessed in F3 offspring on postnatal (P) 9, while the eyes were still closed, using a two-way ANOVA for Treatment and Sex. There was an overall significant effect of Treatment ($F(2,116)=5.24$, $p<0.05$, $\eta^2=0.08$; Figure 3B). Pairwise comparisons demonstrated an effect of ancestral stress in the number of falls off of the tilted platform among females ($F(2,57)=4.43$, $p<0.05$, $\eta^2=0.14$), but not among males ($F(2,54)=2.71$, $p=0.08$, $\eta^2=0.09$; Figure 3B). Follow-up tests showed that the number of falls for TPS females (6.76) was significantly higher than Controls (4.67) but not MPS females (6.63; Figure 3B).

An open field (Figure 3C) was used to assess exploratory activity and response to novelty at the age of P15, just after eye opening was completed. A two-way ANOVA for the number of centre square entries revealed a significant overall effect of Treatment ($F(2,105)=3.46$, $p<0.05$, $\eta^2=0.06$; Figure 3D). A pairwise comparison showed a significant effect of ancestral stress in males ($F(2,50)=4.39$, $p<0.05$; $\eta^2=0.15$; Figure 3D), but not in females ($F(2,55)=0.23$, $p=0.79$, $\eta^2=0.01$). TPS males entered the centre square significantly less frequently (6 entries) than the Control (9 entries) and MPS (8.5 entries; Figure 2D). There was no group difference for the number of wall squares entered.

An automated version of the open field task (Figure 4A) was used to assess exploratory and anxiety-like behaviours in the adult F3 offspring at P110. Centre time and margin time in an open field provide critical measures of anxiety-like behaviours. TPS females spent a total of 22.06 seconds in the centre of the field, while MPS females spent 24.04 seconds, and Controls spent 27 seconds. While there was no overall effect of Treatment in males and females, a pairwise comparison showed a significant decrease in time spent in the centre square in TPS females ($F(2,60)=3.68$, $p=0.03$, $\eta^2=0.11$, power=0.66; Figure 4B). The males showed no significant group difference ($F(2,53)=0.02$, $p=0.98$, $\eta^2=0.001$, power=0.05; Figure 4B), each group spending approximately 32 seconds in the centre square. There was a significant effect of Sex ($F(1,119)=22.67$, $p<0.001$, $\eta^2=0.17$), reflecting that males (32.0 seconds) remained significantly longer in the centre of the open field, compared to females (24.9 seconds).

Vertical activity describes the number of rearing movements during open field exploration. While Control females reared 6.11 times on average, TPS females reared 5.62 times, and MPS females reared 6.57 times. These data represent a significant increase in rearing movements among MPS females compared to TPS females ($F(2,60)=3.97$, $p<0.05$, $\eta^2=0.12$, power=0.690; Figure 4C). However, there was no significant difference in males ($F(2,56)=0.40$, $p=0.67$,

Figure 2: Antepartum F2 generation maternal health outcomes.



A) Maternal weight change during gestation altered by TPS and MPS treatment. B) Gestation length in F2 Control, TPS and MPS dams. C) Resorption rates in F2 Control, TPS, and MPS dams. Error bars show SEM. Asterisk * denotes a significant difference at $p<0.05$.

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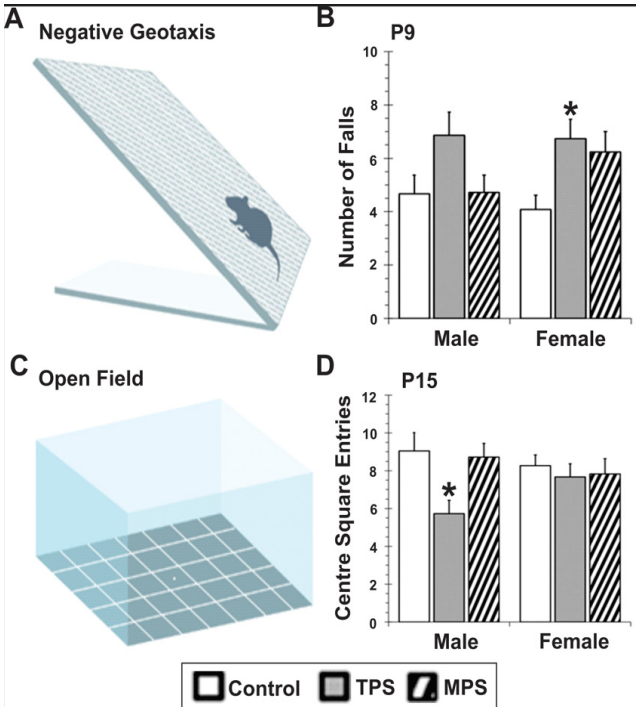
Figure 3: F3 offspring early development.



A) Illustration of negative geotaxis task. B) Number of falls of the inclined platform in F3 male and female offspring at P9. C) Illustration of the open field task. D) Number of entries into the centre square of the open arena field in F3 male and female offspring at P15. Error bars show SEM. Asterisk * denotes a significance of p<0.05.

η^2=0.02, power=0.11; Figure 4C). There was also a significant effect of Sex because females on average reared 6.1 times and males reared only 5.3 times (F(1,119)=17.36, p<0.001, η^2=0.13; Figure 4C).

The Na/K ratio revealed modified stress responses in female F3 offspring

Indicators of HPA axis function in hair were based on the relative sodium (Na) and potassium (K) concentration in F3 male and female offspring. TPS females revealed the highest Na/K ratio of all groups (F(2,29)=4.63, p<0.05, η^2=0.24, power=0.74; Figure 4D), indicating higher HPA axis activation. Sex differences were found due to an overall lower male Na/K ratio of 5.96, and an overall higher female ratio of 8.61 [F(1,65)=29.04, p<0.001, η^2=0.33; Figure 4D].

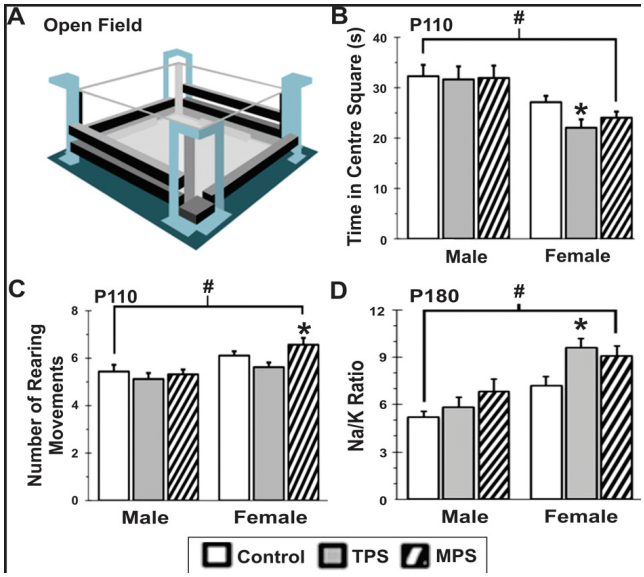
The MSI predicted gestational physiological biomarkers

Pearson's R correlation was used to examine the relationship between the gestational day (G) 11 and G18 MSI and each individual biomarker in order to determine the extent to which each individual marker was contributing to the MSI score (Figure). The MSI at G11 was positively correlated to blood glucose (r= 0.60, p<0.001; Figure 5A) and corticosterone levels (r=0.44, p<0.05), and negatively correlated to weight change (r =-0.48, p<0.01; Figure 5D). At G18 the MSI was still positively correlated to glucose (r=0.49, p<0.01; Figure 5E) and corticosterone (r=0.48, p<0.01; Figure 5F), and negatively correlated to both absolute body weight (r=-0.87, p<0.001; Figure 5G & H) and gestational weight change (r=-0.62, p<0.001).

Maternal biomarkers as predictors of offspring health

The relationship between the individual maternal biomarkers at G11 and G18 and each of the behavioural outcomes in offspring revealed significant changes as a result of ancestral stress (Table 1). Maternal blood glucose levels at G11 were negatively correlated to the vertical exploration in the open field in P110 females (r=-0.52, p<0.05) but not in males (Table 1). Moreover, maternal circulating corticosterone levels at G11 were negatively correlated to the open field centre square entries in P15 males (r=-0.56, p<0.05; Table 1), but not in females. Maternal body weight at G11 was negatively correlated to margin time and positively correlated to centre time in P110 females (margin: r=-0.45, p<0.05; centre: r=0.45, p<0.05; Table 1). Maternal body weight at G18 was negatively correlated to centre square entries in the open field in P15 males (r=-0.56, p<0.05; Table 1), but not in females. Maternal weight change was not correlated to any

Figure 4: Adult F3 offspring behavioural and physiological stress responses.



A) Illustration of an automated open field task. B) Time spent in centre square in the open field in F3 male and female offspring at P110. C) Number of rearing movements in automated exploratory field in F3 male and female offspring at P110. D) Hair Na/K ratio as a function of stress response in F3 male and female offspring at P180. Note that TPS females show the highest Na/K ration of all groups. Error bars show SEM. Asterisk * denotes a significance of p<0.05 between groups, # denotes a significance of a significance of p<0.05 between males and female.

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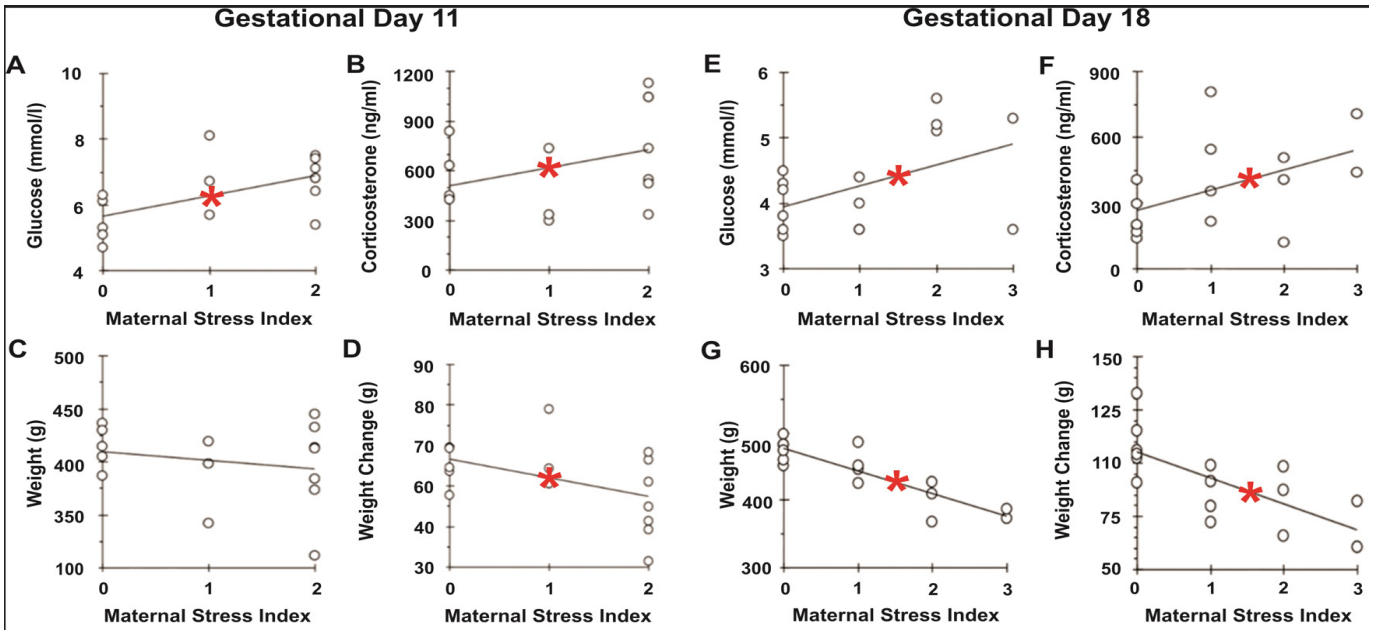
behaviour change at G11 or G18. In summary, these findings reveal that maternal physiological biomarkers may serve as predictors of offspring behavioural outcomes.

Furthermore, Pearson's correlations were used to determine the relationship between G11 and G18 MSI values and offspring behaviour to identify predictors of offspring health trajectories at various ages (Figure 6). The results indicated that the MSI at G11 was negatively correlated to vertical movements in the open field exploration task for P110 males (r=-0.514 p<0.05; Figure 6A & C), but not in females. The MSI at G18 was positively correlated to centre square entries in open field exploration in P9 males (r=0.75, p<0.01), but not in females (Figure 6B & D).

Figure 5: Individual maternal marker contribution to MSI at G11 and G18.



A & E) The relationship between MSI and maternal blood glucose level. B & F) The relationship between MSI and maternal blood corticosterone level. C & G) The relationship between MSI and the maternal body weight. D & H) The relationship between MSI and the maternal weight change. Asterisk * denotes a significance at p<0.05.

Table 1: Correlations demonstrating the relationship between maternal markers collected at gestational days 11 and 18 and offspring behaviours at postnatal days (P) 15 and P110. Neg denotes a negative relationship, pos denotes a positive relationship. Asterisk * denotes a significance p<0.05, and ns denotes a non-significant correlation.

MALE					
Gestational Day 11	Glucose	Number of Rearing Behaviours	P110	Neg	ns
	Glucose	Number of Vertical Movements	P110	Neg	ns
	Body Weight	Centre Time	P110	Neg	ns
	Body Weight	Margin Time	P110	Neg	ns
Gestational Day 18	Glucose	Number of Rearing Behaviours	P110	Neg	ns
	Glucose	Number of Vertical Movements	P110	Neg	ns
	Body Weight	Centre Square Entries	P15	Neg	p<0.05*
	Corticosterone	Centre Square Entries	P15	Pos	p<0.05*
FEMALE					
Gestational Day 11	Glucose	Number of Rearing Behaviours	P110	Neg	p<0.05*
	Glucose	Number of Vertical Movements	P110	Neg	p<0.05*
	Body Weight	Centre Time	P110	Pos	p<0.05*
	Body Weight	Margin Time	P110	Neg	p<0.05*
Gestational Day 18	Glucose	Number of Rearing Behaviours	P110	Neg	p<0.05*
	Glucose	Number of Vertical Movements	P110	Neg	p<0.05*
	Body Weight	Centre Square Entries	P15	Neg	ns
	Corticosterone	Centre Square Entries	P15	Pos	ns

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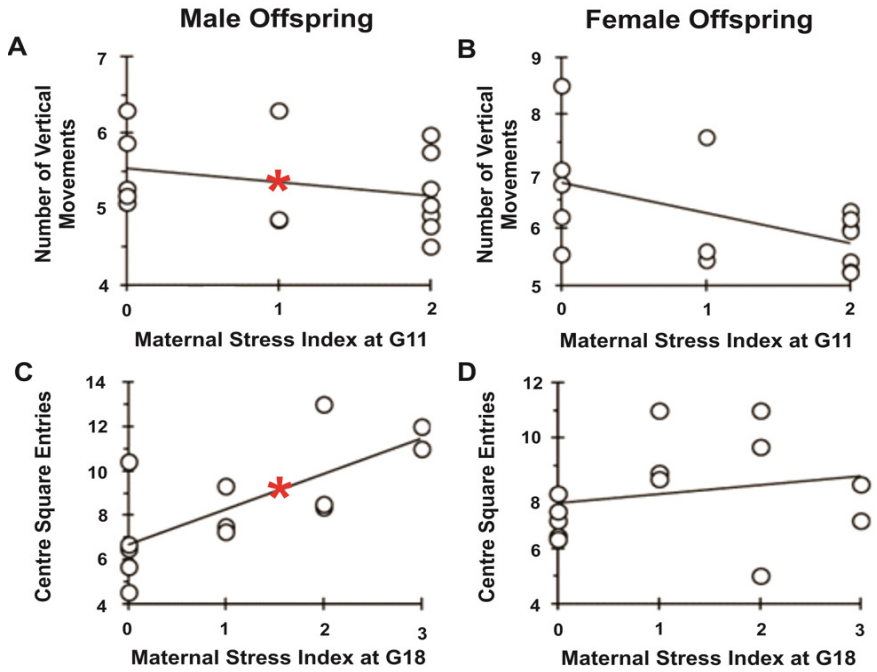

Figure 6: Correlations demonstrating the relationship between MSI at G11 & G18 and behavioural outcomes in F3 males and females.

Discussion

Maternal distress during pregnancy is recognized as one of the main determinants of offspring health. Here we show in a rat model that ancestral maternal prenatal distress reaching back three generations may affect pregnancy outcomes and sex-dependent offspring developmental trajectories. The comparison between a single generational stress exposure (TPS) versus repeated generational stress exposure (MPS) provides a unique framework upon which the cumulative burden of stress can be assessed. Both TPS and MPS induced adverse pregnancy outcomes and delayed offspring development. Despite the limited group size in this proof-of-concept study, the data indicate that maternal physiological biomarkers serve as valuable predictors of pregnancy outcome and postnatal offspring development. In addition, the present findings demonstrate sex differences in response to TPS and MPS as a function of age in the F3 generation. The present data support previous reports showing that ancestral stress [15, 16, 19] and prenatal stress [39-42] program HPA axis sensitivity, thus generating a lasting impact on physiology and metabolism [43]. Even though the present data are based on a limited sample size, the markers indicate changes in glucose, corticosterone, and weight dysregulation due to ancestral stress in both groups, with the largest significant effect observed in the TPS group. Accordingly, other types of gestational stressors have been shown to limit weight gain during pregnancy [44, 45]. Gestational maternal body weight gain also revealed to be a robust predictor of risk taking and affective behaviours in offspring. For example, higher maternal weight at G11 was positively associated with greater risk-taking behaviour in terms of more time spent in the open field centre among adult female offspring. At G18, this association shifted towards higher maternal weight gain predicting lower exploratory activity and lower anxiety-like behaviours in young and adult male offspring. Because higher maternal weight gain may be regarded as an indicator of low maternal stress, this result is opposed to some reports that linked prenatal stress to increased anxiety [22, 53, 54]. The correlational analysis of the longitudinal assessments suggests that maternal metabolic and hormonal status may predict offspring development. For example, maternal gestational glucose levels measured at G11 and G18 predicted adult female offspring exploratory activity levels in the open field. Reduced time in the centre field may serve as an indicator of anxiety-like behaviours [55]. The present study did not differentiate between supported and unsupported rearing movements [55], but one may argue that a higher number of rearing movements may represent a measure of stress-associated hyperactivity [56]. Mothers with elevated glucose levels at G11 had female offspring that were less likely to engage in physical activity themselves, however. These data agree with previous descriptions, showing mothers with gestational diabetes are more likely to have children that are obese or have high blood pressure, or have neurobehavioural changes indicative of anxiety or depression [46-49]. Moreover, higher gestational corticosterone levels on G11 were correlated with higher anxiety-like behaviours,

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as indicated by fewer open field centre square entries in 15-day old male offspring. This finding agrees with previous data and suggests that higher levels of maternal corticosterone are associated with higher levels of anxiety in young male offspring [50, 51], which may disappear with advanced age, however [52].

The finding that TPS dams resorbed their offspring at a higher rate than the control dams is an indication that the mothers were at higher risk of adverse birth effects due to their ancestral stress. Resorption of fetuses during pregnancy particularly in the TPS dams may indicate that the environment initially was assessed as plentiful in resources, but later shifted during gestation, leading to loss of offspring. This problem has been addressed, specifically regarding insects and their clutch size, and is referred to as clutch-size optimization [57]. The surrounding assumption is that there is a negative correlation between the number of offspring, and their corresponding survival, primarily due to resource accessibility [57, 58]. Therefore, a large litter is based on sufficiently abundant environmental resources, as to not limit the growth and development of the offspring. The MSI, calculated as a composite score of behavioural and physiological markers, may represent a valid index for assessing the impact of chronic HPA axis dysregulation in these models. The correlational analysis suggests that at G11, glucose, corticosterone, and weight change were strong contributing factors to the MSI, whereas at G18, maternal weight became a robust predictor of the MSI. The G11 MSI also served as a predictor of exploratory activity in adult females, with a high MSI linked to low rearing activity, whereas the post-stress MSI on G18 was positively related to lower anxiety-like behaviours in young males. The correlational analysis reflects its predictive value for adverse developmental trajectories in the offspring. Including a larger number of variables of maternal health [31] and validating the MSI in additional rodent cohorts may further grow its predictive power. Ancestral maternal stress in the present study was also accompanied by metabolic changes that indicate altered adrenal activity. Hair elemental analysis has become a useful tool to assess metabolic impacts of adverse early life experiences [59]. Metabolic health through hair samples has been pursued previously revealing that advanced age reduces levels of potassium among other elements in rat hair, and that myocardial infarction and renal failure were associated with elevated levels of sodium and potassium [37]. The finding of higher Na/K ratios in female TPS rats is supported by previous observations that stress caused a reduction in Na consumption, and a corresponding reduction in Na excretion [60]. Moreover, it was found that behavioural stress in dogs resulted in antinatriuresis, or a reduction in urine output, and a corresponding decrease in Na excretion [61]. This reduction in mineral excretion through the urine would likely result in accumulation of Na in organs and hair, and it is associated with altered stress response due to hyperactive adrenal glands [31].

Ancestral stress bears the risk of dysregulating the HPA axis in the offspring along with neuronal changes in the prefrontal cortex, hippocampus and amygdala, resulting in long-term alternations in stress reactivity [22]. Nevertheless, developmental programming in response to ancestral stress may be linked to different mechanisms that shape age-dependent stress vulnerability and resilience [21, 22]. For example, Erickson et al. [62] showed that MPS alters exploratory movement patterns particularly in early and late life but appear normal at reproductive age. These findings indicate that early life and older age are particularly vulnerable to the impact of ancestral stress [62]. Overall, the present data propose a higher capacity for stress resilience in the MPS lineage as compared to the TPS lineage. These findings are in line with data showing that recurrent stress exposure in the MPS lineage may promote partial tolerance to lifetime stress and more resilient health trajectories [21, 43]. Specifically, Ambeskovic et al. [22] demonstrated increased levels of anxiety-like behaviours in young adult TPS females but not in MPS females, nor males at P180 as measured in the elevated plus maze [22]. The present longitudinal behavioural profiles in the F3 offspring, however, indicate that both TPS and MPS lineages were vulnerable to anxiety-like changes and altered affective states, while still larger significant effects were seen in TPS offspring. For better interpretation of the present findings, it is important to note the ways in which the nature of ancestral stress in the TPS and MPS lineages differed. The F2 TPS mothers were directly exposed to F0 grandmaternal stress in utero through the gametes [63, 64]. Their F3 offspring, on the other hand, were not exposed directly but influenced by inherited stress-associated epigenetic programming in their F0 great-grandmother. The MPS paradigm, by contrast, exposed each pregnant mother to gestational stress in the F0, F1 and F2 generations. Thus, each MPS generation represents the cumulative prenatal stress burden of their ancestors and associated epigenetic inheritance in combination with their own prenatal stress [65]. It is possible that this repeated presentation of stress is producing partial resilience [21, 64], where prolonged stress can actually encourage resilience through epigenetic preparedness [27, 67]. In this study, the behaviour of MPS animals was mainly comparable to non-stressed controls, indicating potential resilience due to cumulative effects of generational and prenatal stress. These observations are supported by our previous studies showing resilience in F4 female offspring for multiple behavioural outcomes including fine motor function [66] and affective state [21, 22, 62] in adulthood. Notably, multigenerational stress in clinical studies has also been shown as an important moderator of parental trauma effects in the second generations

[68]. The present study provides novel insights into sex differences in maturation from early life to young adulthood in response to ancestral stress. Males generally seemed to be most vulnerable to TPS [19, 22, 69] and MPS [19, 70] at infantile ages while females responded more strongly during young adulthood [20, 22, 71]. These findings are supported by previous reports that in later life, females rather than males show a higher risk of anxiety-related behaviours in the elevated plus maze [72-74], and that prenatal stress in females leads to greater risk to anxiety-like and depression-like behaviours [75]. This result is also supported by human studies, which demonstrate that females are twice as likely to develop depression and anxiety disorders, as compared to males [76-78]. Alternatively, Brunton and Russell [53] observed anxious behaviour solely in 3-month old males after exposure to a stressor, while females either showed no increased anxiety [53] or showed attenuated anxiety-like behaviours [79]. The variability of these findings illustrates that the timing, nature, duration, and intensity of the prenatal stressor, as well as (epi)genetic predisposition determine the outcome and sexual dimorphism of stress-induced outcomes. These findings, however, highlight the value of the use of cumulative stress indices, such as the MSI, which allow to generate an estimate of total stress load at a certain time in life [31] in order to determine the momentary physiological impact of the past lifetime and generational experiences. It needs to be noted that, even when effects are only significant in one sex, the trend frequently seems to be present in the other sex as well. For example, geotaxis results are significant in TPS females at P9 while TPS males display a non-significant trend in the same direction. The non-significant trends may arguably derive from limited sample size and small effect size. Thus, the present sex differences need to be interpreted with caution to prevent misleading conclusions about sex-specific effects.

Ultimately, the present findings support the match/mismatch hypothesis of prenatal stress [24-26], by extending the original concept to a generational context. The classic match/mismatch hypothesis, derived from the developmental origins of health and disease (DOHaD) framework, posits that developmental adaptation to the intrauterine environment predicts the adaptive response to conditions of the postnatal environment [27], thus promoting survival and resilience. Here, we observed that MPS offspring that experienced cumulative generational stress adapted better to challenging behavioural tests, such as a novel open field environment, as opposed to TPS offspring that were subject to stress in one generation only. Thus, the TPS lineage may engage fewer adaptive neural resources in adolescence and young adulthood, suggesting a "mismatch" situation as opposed to a generational "match" situation in the MPS lineage. The present proof-of-principle study suggests that MPS animals, though experiencing more cumulative stress across several generations, adopt mechanisms mediating at least partial stress resilience, which amounts to more positive pregnancy outcomes. Through epigenetic mechanisms, MPS may support the formation of new behavioural traits [20] and coherence between brain areas [80] thus supporting behavioural complexity in a dynamically changing environment, but also coming at the expense of elevated health risks in advanced age [43]. The present data suggest that consequences of mild stress across generations may produce a covert or subclinical phenotype in single behavioural and physiological measures. While behavioural flexibility linked to a subclinical phenotype may be advantageous early in life [16, 20, 22, 71] it may produce wear and tear over time resulting in adverse health consequences later in life [43]. A composite index such as the MSI may provide a more reliable assessment of homeostatic dysregulation linked to cumulative stress than any single parameter. The use of composite indices therefore provides a conceptual framework through which the cumulative physiological burden of past and present adverse experiences can be approximated. This knowledge may facilitate the development of predictive models of lifetime health trajectories within a precision medicine framework.

Declarations

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Conflict of interest/competing interest

The authors declare no conflict of interest or competing interests.

Ethics Approval

All procedures in this study were approved by the University of Lethbridge Animal Care Committee in compliance with the standards set out by the Canadian Council for Animal Care.

Consent to participate: N/A

Consent for publication: N/A

Availability of data and material

Data are available upon request to the authors.

Code availability: N/A

Authors' contributions

TR, MA and GM designed the experiment; TR, MA and EF performed the data collection; TR, MA, EF, and OA

participated in data analysis; TR, MA and GM wrote the manuscript; all authors provided edits and approved the final version of the manuscript.

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