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RESEARCH ARTICLE

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Perceived threats of infanticide reduce maternal allocation during lactation and lead to elevated oxidative damage in offspring

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Abstract

1. Maternal investment is costly to the mother but essential to offspring survival in altrical species. Infanticide by novel males results in loss of maternal investment, and maternal strategies have evolved to mitigate these losses. One such maternal strategy, the Bruce effect, involves spontaneous abortion by females of some mammal species when exposed to a novel male during pregnancy.
2. In mice, the Bruce effect only occurs during early pregnancy, but we have previously found that female mice exposed to a novel male's scent in late pregnancy weaned smaller offspring. Here, we replicate that manipulation to resolve the cause of the reduced weaning weight and subsequent effects on offspring fitness.
3. Females exposed to an unfamiliar male's scent in late pregnancy spent significantly less time nursing their pups during lactation, suggesting that reduced maternal allocation contributes to slower offspring growth. The offspring with a reduced weaning weight exhibited catch-up growth and reached a normal weight at adulthood. These offspring, however, were found to bear oxidative damage in adulthood, revealing long-term effects on offspring condition.
4. We conclude that female mice strategically alter their investment in lactation in relation to the likelihood of infanticide, but that this results in long-term fitness costs to their offspring.

KEYWORDS
catch-up growth, infanticide, maternal effects, oxidative stress

1 | INTRODUCTION

In mammals, reproduction is characterised by large maternal investments in pregnancy, lactation and other behaviours critical for offspring survival, growth and development (Wolff & Sherman, 2008). This investment such as nutrition, warmth and protection can be costly to the mother (Bronson, 1989; Clutton-Brock & Vincent, 1991), and those costs are exacted in the currency of residual reproductive value (König, Riester & Markl, 1988). In general, the relationship between mother and offspring is a cooperative interaction, with the mother benefitting from the success of her progeny. However, with the current and future reproduction known to trade-off (Kirkwood & Austad, 2000; Reznick, 1985; Stearns, 1992), a mother can also benefit from altering, and sometimes reducing, her investment in current offspring according to environmental conditions, to optimise her overall fitness.

In mice (as in most mammals), lactation is the most energetically demanding episode of reproduction (Speakman, 2008) and is a key time to modify investment in relation to contextual conditions. Maternal investment in lactation is somewhat flexible in

mice (König, 1985; König & Markl, 1987), and offspring do not receive more milk than the mother's optimal allocation during lactation, despite frequent suckling attempts (König & Markl, 1987). Other species, such as wild primates, have been observed to alter maternal investment and wean offspring prematurely when an unfamiliar male enters the natal group (Teichroeb & Sicotte, 2008; Zhao, Borries & Pan, 2011). Such flexibility may significantly enhance maternal fitness.

Females have also evolved other strategies to optimise their maternal investment when faced with the prospect of infanticide. Infanticide represents one of the more extreme forms of sexual conflict that results in a significant loss (and waste) of maternal investment for females. Many mammalian species have been documented to commit infanticide, which is thought to be an adaptive strategy for the perpetrator to enhance their reproductive success (Agrell, Wolff & Ylönen, 1998), provide nutritional benefits, increase access to limited resources, increase reproductive opportunities or ensure parental care is directed to the perpetrator's own offspring (Ebensperger & Blumstein, 2007). Social countertactics to infanticide may include forming affiliative relationships with adult males (Borries, Launhardt, Epplen, Epplen & Winkler, 1999; Palombit, 2000; Palombit, Seyfarth & Cheney, 1997; Smuts, 1985; Weingrill, 2000), cooperative defence (see Pradhan & van Schaik, 2008; Teichroeb, Wikberg, Bădescu, Macdonald & Sicotte, 2012; Van Schaik & Janson, 2000), changes in group sex ratio (see Pradhan & van Schaik, 2008; Teichroeb et al., 2012; Van Schaik & Janson, 2000; Van Schaik & Kappeler, 1997) or multiple male mating to confuse paternity (see Van Schaik & Janson, 2000; Wolff & Macdonald, 2004). It is also of note that female infanticide is also common in rodents (Vom Saal, Franks, Boechler, Palanza & Parmigiani, 1995; Ylönen, Koskela, & Mappes, 1997).

The threat of infanticide has also been shown to have effects beyond the killing of the offspring in mice. Parkes and Bruce (1961) reported that recently, inseminated female mice (*Mus musculus*) terminate their pregnancies following the exposure to the urinary scent of an unfamiliar male and return to oestrus. This phenomenon, now known as the "Bruce effect," has been experimentally confirmed in numerous laboratory studies in house mice (Bruce, 1960; Chipman & Fox, 1966) and across a number of murine and microtine rodent species (Clulow & Clarke, 1968; Clulow & Langford, 1971; Mallory & Clulow, 1977). It has also recently been observed in the wild in the primate *Theropithecus gelada* (Roberts, Lu, Bergman & Beehner, 2012).

The Bruce effect only occurs in mice if the female is exposed in early pregnancy, up to 4–5 days postmating (Bruce, 1961), before embryo implantation. We have shown that if female mice are exposed to an unfamiliar male in late pregnancy (approximately day 14), offspring are of comparable birthweight, but growth is slower over lactation, resulting in lighter weaning weights (Gale, Gibson, Brooks & Garratt, 2013) compared with controls. Following weaning however, the experimental offspring grew faster and caught up to the control offspring by the onset of adulthood. Reduced weaning weight is possibly due to alteration of maternal behaviour during lactation. As unfamiliar males typically kill pups sired by another male (Vom Saal, 1985), the females may strategically reduce their investment in lactation to prevent wasting it on "doomed" offspring. If so, females are capable of utilising subtle tactics to optimise their investment in reproduction in relation to their perceived chances of offspring survival. In commensal habitats, mice generally live in groups consisting of a number of breeding females, potentially some nonbreeding females and subordinate males, and a dominant male who aggressively defends his territory against unfamiliar males (Hurst, 1990). As territory turnover does frequently occur (Bronson, 1979; Oakeshott, 1974), these counteradaptations to the infanticide threat the unfamiliar presents are of great advantage to these females. However, whether reduced offspring growth was a consequence of a strategic alteration of investment by mothers in that study is unknown. Other possible causes of the offspring's reduced weaning weight could include stress triggered by the unfamiliar male (stress has previously been found to result in litters with a reduced weaning weight following lactation (Barlow, Knight & Sullivan, 1978; Kinsley & Svare, 1988; Meek, Burda & Paster, 2000)) or an epigenetic modification in offspring gene expression.

Accelerating growth requires an increase in metabolic activity that can damage the organism (Morgan, McCarthy & Metcalfe, 2000). One such cost of accelerated growth, oxidative stress, has been documented in zebra finches (Alonso-Alvarez, Bertrand, Faivre & Sorci, 2007) and damsel flies (De Block & Stoks, 2008). Oxidative stress results from an imbalance between the production of harmful reactive oxygen species (ROS) and an organism's ability to mitigate and detoxify the damaging effects (Monaghan, Metcalfe & Torres, 2009). Failure to moderate this balance can result in oxidative damage to key biological molecules such as DNA, proteins and lipids (Monaghan et al., 2009) and can limit investment in other life-history stages (Costantini, 2008).

Modifications in maternal investment have been found to have further effects other than just a reduced weaning weight. Mouse pups show great developmental plasticity, with various aspects of their early environment affecting their life-history trajectories and having lasting effects on adult phenotypes. Through the influence of maternal effects, mothers may alter the phenotype of their offspring and affect their physiological, sexual and behavioural responses as adults (Rossiter, 1996; Sheldon & West, 2004).

The aims of this investigation were to test whether the degree of maternal investment during lactation is affected by the threat of infanticide and whether any such effects on maternal investment impose further costs to the offspring later in life. We predicted that

1. When females are faced with the threat of infanticide, they will strategically alter investment in their offspring by changing their behaviour during lactation.
2. Offspring that accelerate their growth rate following a reduced weaning weight will suffer oxidative costs as a consequence of the rapid growth.
3. Offspring that have a reduced weaning weight will suffer costs to components of reproductive effort such as scent-marking rates and composition for males and future reproduction for females.

2 | MATERIALS AND METHODS

This study aimed to further investigate the cause of the reduced weaning weight we previously observed in offspring whose mothers had been exposed to a novel male and also test for further effects on the offspring's fitness. To do this, we replicated the experimental manipulation of our previous experiment (Gale et al., 2013) exposing females to either an unfamiliar male or the paternal male late in their pregnancy on three occasions over the last 8 days of gestation. Building on from this previous experiment, we added additional measures to attempt to elucidate the cause of the reduced weaning weight observed in the offspring and attempt to detect any costs of the altered growth rate. We added a third unmated control treatment, in which females were housed with another female instead of a male. The unmated treatment acted as a control for female weight and our marker of stress (glucocorticoid metabolites). We then conducted scan sampling during lactation where we examined female nursing behaviour, collected faecal samples to measure female stress and measured offspring oxidative stress levels at adulthood to test for oxidative damage associated with compensatory growth. We also tested aspects of reproductive fitness in the offspring including scent-marking rates and major urinary proteins (MUPs) in the males, and we mated the female offspring to assess their pup birth and growth rates.

2.1 | Animal housing

Experimental mice were all sixth-generation captive-bred house mice (*M. musculus*) originally derived from a population of wild mice acquired from a chicken farm in the northwest of Sydney, Australia (as in Gale et al., 2013). Females were weaned at 28 days of age and were housed with their female siblings until the beginning of the experiment. Males were also weaned at 28 days of age but were housed individually. Mice were maintained on a 12:12-hr reversed light cycle. A dim red light was used for experimental procedures, which were all undertaken in the dark phase as mice are nocturnal. Each mouse was housed in a 315 × 180 × 125 mm cage lined with corncob bedding and provided with tissues and shredded newspaper for bedding. Vella rat and mouse pellets and water were provided ad libitum.

2.2 | Experimental protocol

To investigate the consequences of a novel male's presence to pregnant females (postimplantation of the embryo), we compared two controls (mated and unmated) with the experimental "novel male" treatment. The unmated control was exposed only to the presence and odour of another unfamiliar female. The mated control or "familiar male" treatment females were mated and then exposed to the scent and presence of the same mate. Our third treatment was the novel male treatment that was experimentally manipulated so that late gestation, the mated females were exposed to the scent and presence of a different male who was unrelated to the mate. Because exposure to this new male was late in pregnancy, well beyond the time frame when a Bruce effect is known to occur in mice, females carried pregnancies through to parturition, therefore allowing us to examine whether females alter their reproductive investment in their offspring and whether this has any long-lasting effects on the offspring (as previously used in Gale et al. (2013).

To begin each treatment replicate, a male (or another female for the unmated control) unrelated to the focal female (all between 80 and 120 days of age) was placed into the focal females' cage for a 2-week mating period. Males were subsequently removed, and the females were transferred to a clean cage. Female weights were recorded every 3 days, and a weight gain of 3 g indicated pregnancy (mean days ± *SE* from reaching the 3 g weight threshold to giving birth for females exposed to the male they mated with: 6.9 ± 1.7; females exposed to an unfamiliar male: 7.1 ± 1.9). As the gestation period of *M. musculus* is 21 days (Jones et al., 2009), when the exposures took place, the females were close to parturition and the embryos had undergone substantial development. When the 3 g weight gain threshold was reached, females were sequentially allocated to a treatment, to either exposure from the paternal male (n = 25) or a novel male (n = 24). The unmated control females had already been assigned to be exposed to another female (n = 25). As the unmated control females did not gain weight concurrent with pregnancy, one unmated control female was randomly assigned to begin their exposure each day that a female from a different treatment hit the weight gain threshold.

The mice (males or females) added to the females' cages were separated by a metal divider with nine small holes (5 mm diameter) which only allowed limited contact. The exposures took place for 3 hr a day for three consecutive days. On each day, a handful of the respective male or female's used bedding (approximately 15–20 g) was placed into the female's cage. Following exposure, the female (prior to parturition) was placed into a clean cage. There were no significant differences between the treatments in the number of days between the removal of the breeding male and the beginning of the male exposure (mean days ± *SE* for females exposed to the male they mated with: 2.16 ± 1.1; an unfamiliar male: 2.08 ± 1.2). There was also no difference in the time between the exposure and the subsequent birth (mean days ± *SE* for females exposed to the male they mated with: 3.2 ± 1.9; an unfamiliar male: 3.7 ± 1.5).

To test for further costs associated with reduced investment during lactation, offspring were tested either for effects to their reproductive fitness or for oxidative damage. At 13 weeks of age, half of the male and female offspring from both treatments were randomly assigned to a reproductive fitness or oxidative stress group. The females in the reproductive fitness group were mated to an unrelated male, and the size, weight and pup mortality were recorded. The males in the reproductive fitness group were tested for scent-marking rates and concentration of MUPs.

2.3 | Maternal investment and offspring weights

The body weights of the females were recorded every 3 days throughout the experiment. Offspring were weighed at birth and

every 3 days during lactation (to the nearest 0.1 g) as a quantification of maternal investment (Ortiz, Boeuf & Costa, 1984; Pontier et al., 1989; Ross, 1988). The offspring were weighed collectively as a litter until weaning (4 weeks of age), after which they were separated from their dam, and an individual weight was recorded. Another individual weight was collected for each of the offspring at adulthood (13 weeks of age).

2.4 | Maternal behaviour

Maternal behaviour was evaluated by observing each of the females using a scan-sampling technique twice a day, every day for the duration of their lactation (4 weeks). Observations were conducted during the dark phase using only a head torch with red light. The first observation occurred in the second or third hour after the change from the light to dark period and the second between 4 hr and 1 hr before the change from the dark to light period. Each of the females was randomly assigned an observation order at the beginning of each observation period, and observations begun 10 min after the red light was turned on to allow them to habituate.

A single observer sequentially recorded each female's behaviour for a total of eight observations with a 5-min gap between each of the eight recordings. As this was done morning and evening of each day, it totalled 16 scans a day. Behaviours recorded included in nest, nursing, grooming, licking pups, eating/drinking, nest building, resting or active (e.g., see (Benus & Rondigs, 1996; Koteja, Garland, Sax, Swallow & Carter, 1999; Palanza, Howdeshell, Parmigiani & vom Saal, 2002). The unmated control females were not included in any of the scan sampling of maternal behaviour.

2.5 | Glucocorticoid metabolites

To determine whether the novel male elicits a stress response from the female, faecal samples were obtained from the females at three points through the experiment and tested for glucocorticoid metabolites (using methods as described by Palme and Möstl (1997). Following a stressful event, glucocorticoids are released into circulation (Sapolsky, Romero & Munck, 2000) and are hence used as an indicator of the stress response. The first sample was taken at the beginning of the experiment (3 weeks prior to being paired for mating), the second on the second day of male exposure and the third on the day 7 of lactation. The unmated females were randomly allocated for faecal sample collection to correspond with the timings of the females in the other treatments.

For collection of faecal samples, mice were placed in a large empty cage (565 × 387 × 203 mm) made from H.D. polyethylene with a wire roof, for a maximum of 45 min. The cages were placed topside down over another corresponding cage, and faecal samples were collected from the bottom cage. Immediately after collection, faecal samples were frozen at −80°C.

Faecal samples were homogenised, and an aliquot of typically 0.05 g faeces (Palme, Touma, Arias, Dominchin & Lepschy, 2013) was extracted with 1 ml of 80% methanol for 30 min on a vortex. When there was insufficient sample, the protocol was adjusted accordingly (e.g., 0.25 g faeces in 2.5 ml methanol). Samples were placed in a spinner overnight, and then, the supernatant was diluted (1:1,000) with assay buffer (Trizma, pH 7.5). Samples were then analysed in a double-antibody 5a-pregnane- 3b,11b,21-triol-20-one enzyme immunoassay (EIA) which has been validated for use in mice to assess the concentration of glucocorticoid metabolites as described by Touma, Sachser, Möstl & Palme, 2003; Touma, Palme & Sachser, 2004.

2.6 | Oxidative stress

At 13 weeks of age, half of the female and male offspring from the novel male and familiar male treatment groups were culled humanely by cervical dislocation, and the liver, kidney, heart and gastrocnemius muscle were quickly removed, snap-frozen in liquid nitrogen and stored at −80°C. To assess oxidative stress in the mice, two biomarkers of oxidation including protein thiol content and aconitase enzyme activity were analysed in each of the tissues (Gibson, Garratt & Brooks, 2015). Both of these biomarkers correlate negatively with oxidative stress.

Protein thiol content was measured by methods described by Di Monte, Ross, Bellomo, Eklöw & Orrenius (1984) but modified for use on a 96-well plate reader (Vasilaki et al., 2006). Protein thiols are essential for the stability of and optimum function of proteins, but are highly susceptible to oxidation (Halliwell & Gutteridge, 1999) and therefore good markers of oxidative stress.

Aconitase is an enzyme of the tricarboxylic acid cycle that is highly susceptible to deactivation by radical oxygen species (specifically superoxide) and therefore used as a marker to indicate levels of ROS and concomitantly oxidative stress (Gardner, 1997; Gardner, Raineri, Epstein & White, 1995; Hausladen & Fridovich, 1994, 1996). As aconitase is located in part in the mitochondria (Gardner et al., 1995; Wiegand & Remington, 1986), mitochondrial density was also assessed using citrate synthase activity. Citrate synthase is an enzyme commonly used as an indicator of the content of intact mitochondria (Holloszy, Oscai, Don & Mole, 1970) and was measured in homogenates according to Pichaud et al. (2008).

2.7 | Offspring reproductive fitness

Dominant adults are known to scent mark more regularly than subordinates (Drickamer, 1995) to communicate their territorial and sexual status (Bronson, 1979; Hurst et al., 2001) and competitive ability (Rich & Hurst, 1998). These chemical scent marks are of high importance to male fitness as they directly influence the attractiveness of a male to a female (Rich & Hurst, 1998). The main involatile scent component of male mouse urine is MUPs that bind volatile components of the urine and slowly release them from the scent marks (Hurst, Robertson, Tolladay & Beynon, 1998). Scent marks may not prevent intruders invading the territory, but they do allow males to use long-lasting signals of identity and dominance over a territory to

alert competitors and potential mates (Hurst & Beynon, 2004; Hurst et al., 1998). Therefore, both the rates and the composition of scent marks can substantially influence male reproductive fitness.

2.7.1 | Scent-marking rates

Scent-marking rates of all of the individually housed male offspring were assessed at 13 weeks of age. Scent-marking rates were measured by placing the individual males into an empty (315 × 180 × 125 mm) cage lined with Benchkote for 1 hr a day, for three consecutive days. The scent marks were measured by the number of spatially separate marks observed under UV light, and the average number of marks for each male over the three trials was used for analysis.

2.7.2 | MUPs concentration

A urine sample was collected from each of the male offspring at 13 weeks of age. Males were confined in a large empty cage (565 × 387 × 203 mm) made from H.D. polyethylene with a wire roof, for maximum of 180 min. The cages were placed topside down over another corresponding cage to allow the mouse urine to pool in the bottom cage. Urine was then pipetted into an Eppendorf tube and frozen at −20°C. The concentrations of MUPs were established using Coomassie Plus® protein assay reagent kit from Perbio Science UK Ltd (Cramlington, Northumberland, UK) as described by Cheetham, Smith, Armstrong, Beynon and Hurst (2009). We also measured urinary creatinine (Beynon & Hurst, 2004) using the method of Cheetham et al. (2009) to correct for the urinary dilution.

2.8 | Statistics

All statistical analyses were performed using SPSS software package version 2.1 (IBM Corp, Armonk, NY, USA). The analyses were conducted with dam ID and experimental block fitted as random factors to account for nonindependence of individuals originating from the same litter and time differences of each group of experimental mice unless otherwise described. For the oxidative stress data, we also fitted plate number as a random factor to control for between-plate variability. Scent-marking frequency was transformed to log $(x + 1)$ to account for measures of zero deposits and normalise the data. Significance was determined at $p \leq 0.05$.

3 | RESULTS

3.1 | Offspring weight

In the novel male treatment, the females gave birth to pups that were of similar weight and litter size as the familiar male treatment females (i.e., exposed to the paternal male). Of 25 females mated in the familiar male treatment, 23 mothers gave birth within the time frame with a mean litter size of 4.217 ± 0.77, and of 24 mothers in the novel male treatment, 21 gave birth within the time frame with a mean litter size of 4.14 ± 0.89. The mean birthweight of novel male treatment pups (1.619 ± 0.432 g) was not significantly different from that of the familiar male treatment (1.628 ± 0.433 g; ANOVA: weight: $F_{1,182} = 0.022$, $p = 0.882$; litter size: $F_{1,42} = 0.070$, $p = 0.792$). Two females in the control treatment and one female in the experimental treatment group destroyed their litters within 3 days of giving birth. Some pup mortality of unknown cause was observed over lactation; however, this is common in captive breeding mice (Weber, Algers, Hultgren & Olsson, 2013). The pup mortality was not significantly different between the treatments (ANOVA: $F_{1,7} = 0.778$, $p = 0.407$) with six mothers of the novel male treatment committing maternal infanticide (totally 10 pups lost) and three mothers of the familiar male (totally seven pups lost).

Although the novel male treatment females gave birth to pups of a similar weight and litter size as the familiar male treatment females, novel male treatment litters grew more slowly over lactation. To analyse the differences in offspring growth rate, we used repeated-measures ANOVA reporting within-subjects effects. Mauchly's test of sphericity indicated that the assumption of sphericity had been violated ($\chi^2(2) = 34.210$, $p = <0.001$); therefore, degrees of freedom were corrected using Greenhouse–Geisser adjusted degrees of freedom. There was a difference in growth rate between the treatments, but there was no effect of sex (treatment: $F_{1.7,310} = 7.49$, $p = 0.001$; interaction between treatment and time: $F_{1.7,310} = 5668$, $p = <0.001$; sex x treatment: $F_{1.6,306} = 1.3$, $p = 0.270$). This resulted in novel male treatment pups being significantly smaller (7.19 ± 0.61 g) at weaning (4 weeks of age) (ANOVA: $F_{1,182} = 27.11$, $p = <0.001$) than the familiar male treatment pups (7.99 ± 1.48 g) (see Figure 1). This difference did not persist into adulthood however, as both males and females of the novel male treatment exhibited catch-up growth following weaning and there were no weight differences at adulthood (13 weeks of age) (ANOVA: $F_{1,184} = 0.760$, $p = 0.384$) (see Figure 2). There were also no significant interactions between treatment and sex in weight

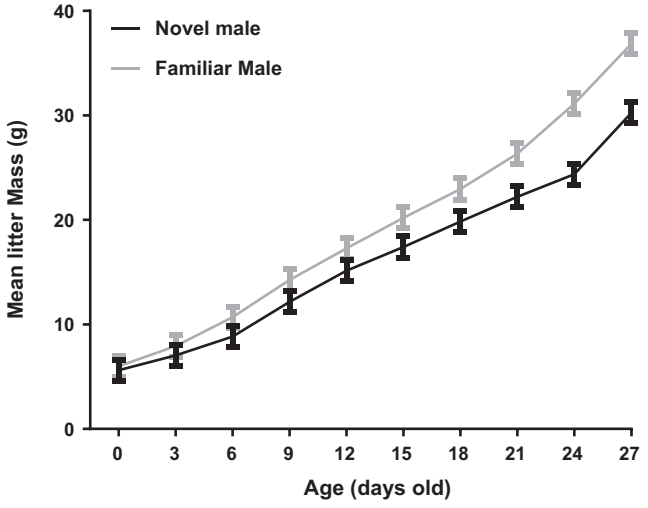

FIGURE 1 Average litter growth rate over lactation (4 weeks). Data are displayed as mean ± *SEM*

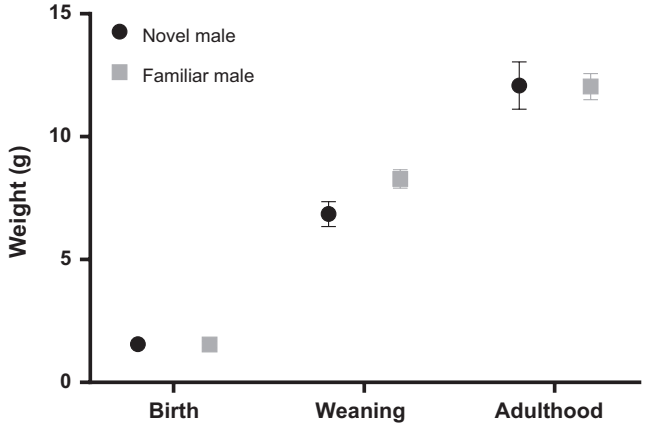

FIGURE 2 Comparison between individual offspring birth, weaning and adult weight between the two treatments. Data are displayed as mean ± 3 *SEM*

at weaning (sex x treatment $F_{1,180}$ = 2.14, p = 0.145) or at adulthood (sex x treatment $F_{1,180}$ = 0.044, p = 0.868)).

3.2 | Maternal behaviour

There was no significant difference in the amount of time the mothers spent in nest, grooming, licking pups, eating/drinking, nest building, resting or active (Table 1). The only behaviour showing significant differences between treatments was nursing, with females exposed to familiar males spent almost twice the time nursing (Table 1).

3.3 | Glucocorticoid metabolites in mothers

Three faecal samples were taken from each female: The first sample was taken before the experiment began to determine the normal level of faecal glucocorticoid metabolites (FGMs) for each female. The second collection was taken on day 2 of the exposures to a male and the third coincided with mid-lactation in the mated treatments. Some of the females did not provide a sample within the time frame they were in the collection cages (45 min), so the sample sizes for the glucocorticoid metabolites are novel male n = 20, familiar male n = 21 and unmated control n = 18. Using a repeated-measures ANOVA, we found that FGMs did change significantly over time (effect of time: $F_{2,112}$ = 131, p = <0.001; interaction between time and housing companion: $F_{4,112}$ = 29.5, p < 0.001). In the novel male and familiar male treatments, the FGMs were higher in the second collection and dropped back down closer to their normal levels of FGMs at the third collection. There was no difference in the FGMs in the females before the beginning of the experiment (ANOVA: $F_{2,56}$ = 0.094, p = 0.911), but there was the following exposure to their partners (ANOVA: $F_{2,56}$ = 43.72, p =<0.001) and at the end of the experiment which coincided with mid-lactation for the reproducing treatments ($F_{2,56}$ = 4.6, p = 0.014)(See Figure 3). After removing the unmated control from the analysis, we found that the effect of time was still significant ($F_{2,78}$ = 143, p = <0.001), but there was no interaction between time and housing companion ($F_{1,78}$ = 1.89, p = 0.158). While there was no difference between the FGMs between the novel male treatment and the familiar male treatment, there was a difference between the mating treatments and females who were not mated. Females from both mated treatments experienced a rise in FGM levels in the second collection following exposures to a male; however, by the third collection at mid-lactation, their FGMs had returned closer to their normal level (collection one). The unmated control females' FGM levels did not show any pronounced variability over the three collections.

3.4 | Oxidative stress in offspring

Both markers of oxidative stress showed consistent evidence of oxidative damage with the novel male treatment (n = 47) in two (liver and heart) of four organs tested having lower protein thiol concentrations and aconitase enzyme activity (indicating higher levels of oxidative damage) than the familiar male treatment (n = 38). There was an effect of sex with novel male treatment offspring males having lower protein thiol concentrations than those of the familiar male treatment males in the heart but there were no other sex

TABLE 1 Maternal behaviour of novel male treatment and familiar male treatment females over lactation

Comparison of the number of times maternal behaviours were recorded during lactation							
				Mated control		Novel male	
	F	*df*	*p*	Mean	*SE*	Mean	*SE*
In nest	3.77	1,41	0.059	114.34	4.15	103.47	3.54
Nursing	11.56	1.41	0.002	15.52	1.34	8.4	1.53
Licking pups	1.79	1,41	0.188	1.82	0.63	0.80	0.34
Nest building	0.12	1,41	0.730	0.65	0.27	0.80	0.31
Eating/drinking	0.14	1,41	0.707	5.82	0.62	5.52	0.52
Grooming	0.14	1,41	0.705	9.73	0.68	10.14	0.82
Active	0.78	1,41	0.382	131.34	6.21	139.76	7.45
Resting	1.15	1,41	0.288	168.73	5.00	179	7.96

differences in any of the analyses for oxidative damage (see Table 2 and Figures 4 and 5).

The same trend was observed when testing the ratio of aconitase enzyme activity to citrate synthase activity (mitochondrial density) ratio. The liver and heart in the novel male treatment were also found to have a significantly lower aconitase enzyme activity to citrate synthase activity ratio indicating higher levels of ROS production in these organs. This decrease in aconitase enzyme activity was not observed in either the kidneys or the gastrocnemius, and there were no effects of sex (See Table 2 and Figures 4 and 5).

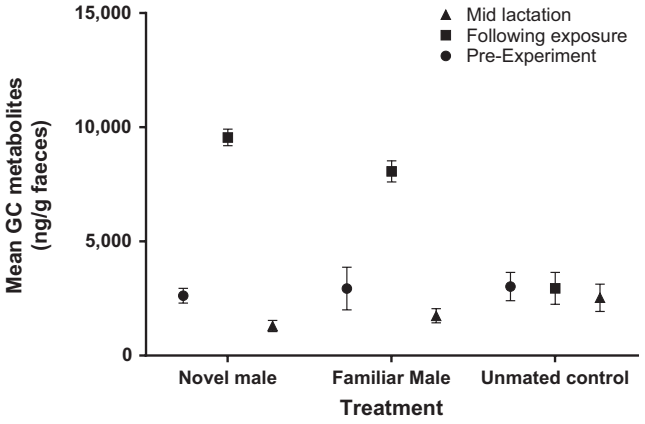

FIGURE 3 Concentration of faecal glucocorticoid metabolites in females taken before the beginning of the experiment, on the second after exposure to a male/female and then mid-lactation in the mated treatments. Females were either exposed to a novel male (novel male treatment) their mated male (familiar male) or another female (unmated control). Data are displayed as mean ± *SEM*

3.5 | Male and female offspring fitness components

For the male offspring fitness components, sample sizes were both $n = 17$ for the treatments. There was no difference in the concentration of MUPs among the male offspring produced by the novel male treatment females compared to the control offspring (ANOVA: $F_{1,30} = 0.76$, $p = 0.543$). The mean (mg/mg creatinine) ± *SE* for the novel male treatment was 18.44 ± 3.60 and that of the familiar male treatment males was 20.73 ± 2.74. Experimental block also did not have an effect (ANOVA: $F_{1,30} = 5.8$, $p = 0.249$). The scent-marking frequency's mean ± *SE* for the novel male treatment offspring was 28.28 ± 10.54 and that of the familiar male treatment males was 36.96 ± 10.49. A repeated-measures ANOVA found that there was no difference in the frequency of scent marks between the treatments ($F_{2,64} = 3.00$, $p = 0.57$). For the female offspring produced that were bred at adulthood, there was no difference in the pup weights that the female offspring gave birth to (ANOVA: $F_{1,40} = 0.35$, $p = 0.556$) or of their pups' weaning weights at the end of lactation ($F_{1,40} = 1.002$, $p = 0.323$) and a repeated-measures ANOVA showed there was no difference in growth rate between the treatments (sex × treatment $F_{1,41} = 1.29$ $p = 0.262$). The mean birthweights between the treatments were 1.26 ± 0.04 g and 1.355 ± 0.13 g for the novel male and familiar male treatment females, respectively, and the mean weaning weights were 12.75 ± 2.09 g and 12.27 ± 0.13 g, respectively. Experimental block also had no effect (ANOVA: $F_{1,40} = 0.69$, $p = 0.837$).

TABLE 2 Markers of oxidative stress in offspring of both treatments at adulthood showing protein thiol concentration (μmol/g protein) and aconitase enzyme activity/citrate synthase (units/mg protein). Models were also fitted with plate number and block as a random factor to control for variation between assay plates

Oxidative stress results for protein thiol concentration and aconitase enzyme activity												
	Liver						Kidney					
	Protein thiol concentration			Aconitase enzyme activity			Protein thiol concentration			Aconitase enzyme activity		
	F	*df*	*p*	*F*	*df*	*p*	*F*	*df*	*p*	*f*	*df*	*p*
Treatment	60.65	1, 80	<0.001	14.1	1, 81	<0.001	1.44	1, 80	0.234	1.47	1,80	0.228
Sex	0.130	1, 80	0.719	0.20	1, 81	0.656	0.01	1, 80	0.997	0.32	1,80	0.569
Sex × treatment	1.43	1, 80	0.234	1.59	1, 81	0.210	0.61	1, 80	0.436	1.85	1,80	0.177
	Heart						Gastrocnemius					
	Protein thiol concentration			Aconitase enzyme activity			Protein thiol concentration			Aconitase enzyme activity		
	F	*df*	*p*	*F*	*df*	*p*	*F*	*df*	*p*	*F*	*df*	*p*
Treatment	10.34	1, 80	<0.001	20.42	1, 81	<0.001	0.17	1, 80	0.681	1.76	1, 80	0.188
Sex	8.49	1, 80	0.005	0.98	1, 81	0.755	2.88	1, 80	0.093	0.78	1, 80	0.379
Sex × treatment	1.80	1, 80	0.183	0.41	1, 81	0.523	0.001	1, 80	0.971	2.11	1, 80	0.150

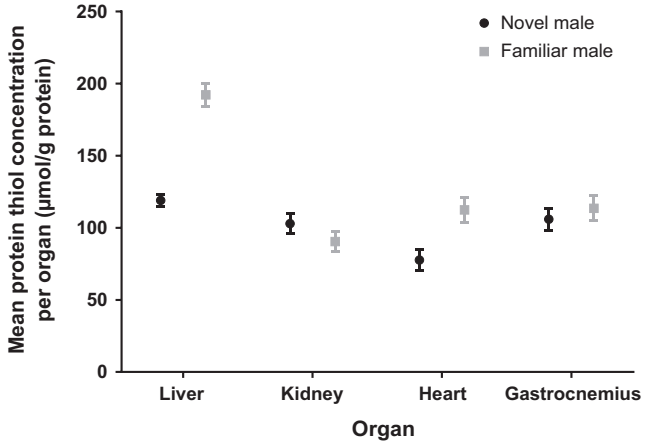

FIGURE 4 Mean protein thiol concentrations. Data are presented as estimated marginal mean ± 1 *SEM* for each measure from generalised linear mixed models for each tissue sample

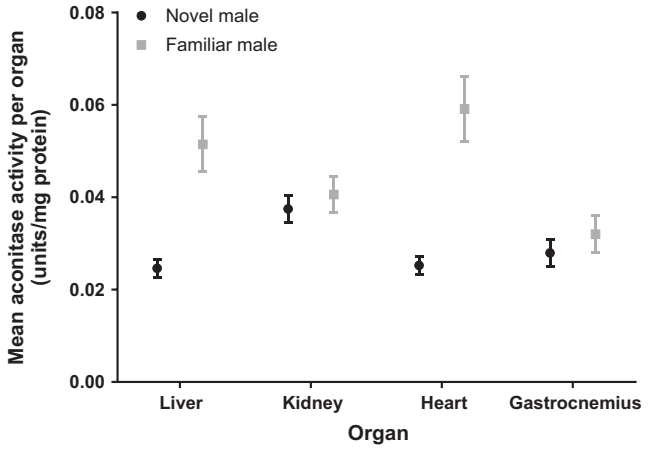

FIGURE 5 Ratio of mean aconitase enzyme activity to citrate synthase activity. Data are presented as estimated marginal mean ± 1 *SEM* for each measure from generalised linear mixed models for each tissue sample

4 | DISCUSSION

Our results support the prediction that the "late Bruce effect," in which female mice exposed to a novel male late in pregnancy weaned at lower weights (Gale et al., 2013), may be due to a strategic reduction in maternal investment in lactation. It is notable that females exposed to a novel male's scent spent less time nursing pups than females exposed to the scent of their mate. Our results support the prediction that females adjust postpartum investment in relation to pups' perceived chances of survival, potentially benefitting maternal lifetime fitness at the expense of the current litter of offspring (Marshall & Uller, 2007).

This finding suggests that patterns of postpartum investment can be adjusted by mothers in relation to the risk of infanticide, in ways that mirror the strategic, spontaneous abortion of pups under the Bruce effect (Bruce, 1960, 1961; Hrdy, 1979; Schwagmeyer, 1979; Storey, 1986), as well as evidence that a mechanism to abort foetuses strategically at the later stages of pregnancy has evolved in other species including the gelada (Roberts et al., 2012) and prairie vole (Clulow & Clarke, 1968; Clulow & Langford, 1971). As mice are only able to abort in early pregnancy, altering their investment postpartum provides an opportunity to respond to the threat of infanticide.

Other studies have shown that female mice strategically moderate investment during lactation and that they may alter investment relative to the reproductive value of their offspring. Mashoodh, Franks, Curley, and Champagne (2012) found that females increased their investment during lactation when mated with a male housed in lifelong socially enriched conditions compared with females mated with males housed in impoverished conditions. This suggests that females may invest more in offspring on the basis of paternal condition. König and Markl (1987) showed that despite frequent suckling attempts, offspring do not receive more milk than is optimal for the mother to provide during lactation, suggesting mothers have control over reproductive allocation during lactation.

Another potential cause of the reduced weaning weight could be a stress response. In rodents, maternal stress has been previously found to cause depressed growth in offspring (Barlow et al., 1978; Kinsley & Svare, 1988; Meek et al., 2000). Previous research on the effects of prenatal stress on offspring is frequently contradictory. The nature, timing and length of the stress inflicted vary from study to study, as do the results. One study, for example, that used crowding as a stressor found no difference in time spent nursing between stressed and nonstressed dams (Moore & Power, 1986), while another study that used novelty stress found that stressed dams spent significantly more time nursing compared to nonstressed dams (Muir, Pfister & Ivinskis, 1985). It is also important to note there is evidence that maternal stress leads to faster (Dantzer et al., 2013) and increased growth of offspring at birth and weaning (Szuran, Zimmerman, Pliska, Pfister & Welzl, 1991).

We found while females all had similar stress levels before the experiment began, females that were mated and then exposed to either a novel or their mated male had significantly higher FGMs than the females that were not mated in the experiment. Females from the mated treatments both displayed a rise in their FGMs following the exposures, suggesting that the females were equally stressed by encountering the paternal male as they were a novel male. Higher levels of FGM could also result from exposure to a male, and as our experiment used another female as an unmated control, we are unable to distinguish this result properly. Only one other study we could find used a novel male conspecific as a source of stress. Lerch, Dormann, Brandwein, Gass and Chourbaji (2016) stressed pregnant or lactating females using unfamiliar male faeces and examined maternal and offspring behaviour to investigate whether early adverse experiences elevate the risk of developing psychiatric disorders. However, unlike our study that used a familiar male as a control, they compared pregnant or lactating females exposed to unfamiliar male faeces with a control group that did not receive any faeces. The scarcity of research that

uses another conspecific as a stressor is surprising as this could be expected to be a more environmentally relevant challenge that other manipulations like forced immobilisation challenge, for example. While the overproduction of maternal glucocorticoids can be harmful (Korgun, Ozmen, Unek & Mendilcioglu, 2012), levels are known to increase during pregnancy in mice (Barlow, Morrison & Sullivan, 1974; Dalle, Giry, Gay & Delost, 1978) as they are essential for foetal development (Korgun et al., 2012). Postpartum, glucocorticoids also have important roles in milk secretion and lactogenesis (Chida et al., 2011). The higher FGM levels that we found in females from both of the mated, compared to the unmated, treatment, may therefore be just a normal consequence of pregnancy.

As in our previous study (Gale et al., 2013), the offspring of the females that were exposed to the novel male were smaller at the end of lactation, but they caught up in size by maturity. The catch-up growth exhibited by the offspring coincides with the time after lactation when offspring begin to feed themselves on solid food. Offspring can acquire the resources to accelerate their growth rate themselves. For compensation or catch-up growth to occur, the benefits must outweigh the costs of not accelerating growth. While there may be a positive association between size and fitness (Roff, 1992) and accelerated growth may increase overall reproductive success, many studies have found that compensatory growth inflicts various costs over different time-scales (reviewed in Metcalfe and Monaghan (2001)). Costs that have been documented in rats (*Rattus norvegicus*) include deficiencies in protein maintenance (Samuels & Baracos, 1995), telomere abrasion rate (Jennings, Ozanne, Dorling & Hales, 1999), insulin regulation (Ozanne & Hales, 1999), adult obesity (Waterland & Garza, 1999) and, perhaps most importantly, reduced life span (Jennings et al., 1999; Rollo, 2002). While compensatory growth may reduce life span, it could still be adaptive if it increases overall reproductive success (Metcalfe & Monaghan, 2001) or short-term survival chances (Arendt, 1997). In mice, reproductive allocation in adulthood is influenced by size, and so compensatory growth may allow individuals to attain a normal reproductive rate in adulthood, at least early in life. Female offspring that exhibited catch-up growth produced litters of the same size and weight as those female offspring from the control group; male offspring showed equivalent scent-marking abilities in our assays. Thus, catch-up growth seems to allow offspring to attain a similar reproductive output early in life that is comparable with the steadier growth in the familiar male group, although costs may be paid for this in terms of late-life reproduction or life span.

The existence of compensatory and catch-up growth shows that organisms do not grow at their maximal rate, but rather at a rate influenced by, and potentially optimised to, their circumstances. Hector and Nakagawa (2012) distinguish these two terms by defining compensatory growth as a faster than usual growth rate and catch-up growth an attainment of control size. Mangel and Munch (2005) propose that growth leads to an accumulation of damage at the cellular level that is expressed at the level of the organism and is an important cost of compensatory growth. We tested for damage on a cellular level in the form of oxidative damage and oxidative stress. We found evidence for oxidative damage in the livers and hearts of offspring from the novel male exposure treatment, highlighting that an olfactory change in a pregnant mother's environment can elicit a variety of maternal and offspring responses, ultimately influencing offspring physiological condition in adulthood. This may be a consequence of catch-up growth, but could also be a consequence of odour exposure itself or changes in maternal allocation in response to this. In future studies, it may be of interest to limit an offspring's ability to show compensatory growth (through a nutritional or genetic manipulation) and test whether oxidative damage in offspring still occurs in adulthood.

Wild mice are highly territorial, and turnover of the dominant male is a common occurrence in wild populations (Bronson, 1979; Oakeshott, 1974). For the females in the territory, that means that they will be exposed to novel males which present the threat of infanticide (Ebensperger, 1998). Our experiment was designed with the rationale to mimic this turnover by exposing the females to a novel male to see the effects it would have on reproductive allocation and offspring fitness. Our results suggest that the very prospect of male territorial turnover can have physiological consequences for the offspring and potentially alter their life history. We also suggest that females are capable of strategically modulating their investment relative to their current contextual conditions, which may offer significant fitness benefits in the wild where offspring survival is much more variable and infanticide is a common threat.

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CONFLICT OF INTEREST

There are no competing interests to declare.

AUTHORS' CONTRIBUTION

T.G., M.G. and R.C.B. conceived the ideas and designed methodology; T.G. collected the data; T.G., M.G. and R.C.B. analysed the data; T.G. wrote the manuscript. All authors, T.G., M.G. and R.C.B. contributed critically to the drafts and gave the final approval for publication.

DATA ACCESSIBILITY

We have archived our data on Dryad. A dataset for this experiment is available from the Dryad Digital Repository https://doi.org/10.5061/dryad.762k24f. (Gale, Garratt, & Brooks, 2018).

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