

ECOLOGY OF STRESS

Maternal adversity and ecological stressors in natural populations: the role of stress axis programming in individuals, with implications for populations and communities

Oliver P. Love^{1*}, Patrick O. McGowan² and Michael J. Sheriff³

¹Department of Biological Sciences, University of Windsor, 401 Sunset Avenue, Windsor, Ontario, N9B 3P4 Canada;

²Department of Biological Sciences, University of Toronto Scarborough, 1265 Military Trail, Toronto, Ontario, M1C 1A4 Canada; and ³Institute of Arctic Biology, University of Alaska Fairbanks, 902 N. Koyukuk Dr., Fairbanks, Alaska, 99775 USA

Summary

1. Biomedical researchers have long appreciated that maternal stressors can induce preparative and adaptive programming in offspring via exposure to maternal Glucocorticoids (GCs). However, few ecologists are aware of the capacity for maternal GC exposure to translate ecological and environmental stressors into preparative and adaptive programmed offspring responses in free-living systems. We review a growing body of experimental work indicating that circulating maternal GCs link ecological stressors with adaptive programming of the stress axis. Throughout, we emphasise that natural and human-induced ecological stressors play a fundamental role in programming the capacity of individuals, populations and communities to respond to both predictable and unpredictable ecological change via translating maternal adversity into responsive programming of the vertebrate stress axis.

2. To encourage rigorous testing of this paradigm in a broad range of ecological systems, we introduce the principal extrinsic stressors with a recognised potential to alter maternal circulating GC levels. We then review from the biomedical literature regarding the underlying physiological and epigenetic mechanisms of stress-induced programming of individual phenotypes to predict how variation in ecological stressors can produce individual variation in stress axis management.

3. To appreciate the potential evolutionary inertia (i.e. adaptive value) of maternally programmed individual variation, we review key recent studies in free-living systems that test its adaptive function, and then discuss how variation in stress-axis programming may scale up to influence populations and ecological communities.

4. Given the huge potential of this field, it is encouraging that ecologists are beginning to examine how and why maternal GCs translate ecological and environmental stressors into preparative stress axis programming in free-living systems.

Key-words: corticosterone, cortisol, ecological stressor, individual variation, maternal adversity, maternal programming, maternal stress, stress axis

Introduction

Ecologists are well aware that Glucocorticoid ('stress' – GC) hormones have the potential to mediate the link

*Correspondence author. E-mail: olove@uwindsor.ca

All authors have contributed equally to the preparation of this document.

between environmental variability and variation in the behaviour, life-history strategies and fitness of a large variety of organisms (Wingfield & Sapolsky 2003; Boonstra 2005; Reeder & Kramer 2005; Wikelski & Cooke 2006; Love & Williams 2008a; Romero, Dickens & Cyr 2009; Sheriff, Krebs & Boonstra 2009). Indeed, the highly conserved nature of the mechanistic functioning of the

hypothalamus-pituitary-adrenal ('stress') axis across vertebrate taxa underscores the biological importance of optimal GC management (Boonstra 2005; Wingfield 2005; Breuner, Patterson & Hahn 2008). The release and management of circulating GCs plays two very important, evidently adaptive, biological roles in vertebrates: baseline GC levels maintain homeostatic energetic balance and are involved in normal day-to-day activities associated with the diurnal cycle (reviewed in Landys, Ramenofsky & Wingfield 2006); meanwhile the acute, 'stress-induced' release of GCs mediates physiological and behavioural responses to environmental challenges (Breuner, Patterson & Hahn 2008). Output from the stress axis begins with sensory input on environmental variation into the hypothalamus and ends with the release of GCs in the form of cortisol or corticosterone (Breuner, Patterson & Hahn 2008). Given the important maintenance and response roles, variation in GC secretion is expected to be a major factor regulating the energetic and life history trade-offs that produce optimal investment decisions and ultimately drive variation in fitness (Hadany *et al.* 2006; Bonier *et al.* 2009). Determining how the interaction between intrinsic state and extrinsic environmental factors produces widespread, and apparently adaptive, intra-specific variation in the functioning of the stress axis is therefore an important goal for evolutionary and physiological ecologists (Love *et al.* 2009; Sheriff, Krebs & Boonstra 2010).

Related questions have been a focus of interest by biomedical researchers studying mechanisms conferring inter-individual variation in disease susceptibility (McGowan & Szyf 2010b). In the human literature, epidemiological studies during early life have provided considerable evidence that environmental factors can alter health trajectories (Low, Gluckman & Hanson 2012). Barker's 'thrifty phenotype' hypothesis proposed that maladaptive outcomes were the result of a mismatch between conditions of low food availability during development and actual environmental conditions of adequate nutrition (Hales & Barker 1992). This stimulated considerable research on human responses to a range of environmental conditions during development that influence human health trajectories in a manner consistent with that of an adaptive response, chief among them were effects of nutrition and parental care (Gluckman, Hanson & Spencer 2005a; Low, Gluckman & Hanson 2012). Biomedical studies of humans and laboratory animals indicate a profound effect of early life parental care on the epigenetic programming of the stress axis and associated behaviours (McGowan *et al.* 2008, 2009, 2011).

The capacity for maternal GC exposure to translate ecological and environmental stressors into programmed responses in offspring (size, growth and performance) has been well documented in free-living systems across four diverse taxa (birds: Love *et al.* 2005; Love & Williams 2008b; mammals: Sheriff, Krebs & Boonstra 2009, 2010; reptiles: de Fraipont *et al.* 2000; Meylan *et al.* 2002; Meylan & Clobert 2005; fish: McCormick 1998, 1999, 2006).

Maternal stress can also significantly alter the ability of offspring to respond to future ecological stressors via programming effects on the stress axis (Hayward *et al.* 2006; Love *et al.* 2008; Sheriff, Krebs & Boonstra 2010; Haussmann *et al.* 2012), something that medical and laboratory mammalian researchers have long appreciated given that the embryo/foetus and post-natal offspring must balance immediate physiological and developmental challenges with appropriate preparation for adult life (reviewed in: Seckl 2001, 2004; Seckl & Meaney 2004; Gluckman *et al.* 2005b; Macrì & Wu rbel 2006; Meaney, Szyf & Seckl 2007). As such, much of our discussion will focus on the organisational effects of hormones (i.e. the effect of a hormone to permanently organize a system), rather than the activational effects of hormones (i.e. the effect of a hormone on a system that has already developed), given that organisational effects are expected to have stronger and longer-term effects on fitness (Williams 2008).

Contemporary experimental research suggests that a variety of ecological stressors, acting via maternally derived stress during reproduction, can phenotypically alter the stress-axis of offspring: environmental effects on maternal state (Love & Williams 2008a), predation pressure (Sheriff, Krebs & Boonstra 2010), quality of the rearing environment (Love, Bird & Shutt 2003; Pravosudov & Kitaysky 2006) and even the unpredictability of the social environment (Landys, Goymann & Slagsvold 2011). Moreover, permanent programming of the stress axis (as opposed to reversible developmental flexibility, i.e. Lendvai *et al.* 2009) suggests that effects are not just unavoidable developmental costs, but rather adaptive responses that prepare individuals to behaviourally cope, reproduce and survive in environments where ecological stressors are frequently encountered, or are greater in intensity (Meylan & Clobert 2005; Love & Williams 2008b; Preisser 2009; Sheriff, Krebs & Boonstra 2010).

Here we review a growing body of experimental research testing the hypothesis that circulating maternal GCs link ecological stressors with adaptive programming of the vertebrate stress axis in free-living systems. To encourage rigorous testing of this hypothesis in a broad range of ecological systems, we briefly review extrinsic stressors with a recognised potential to alter maternal circulating GC levels. We then explore how pre-natal exposure to maternal GCs, or to GC-altered post-natal maternal behaviour, affects the underlying physiological and epigenetic mechanisms driving stress-induced programming of individual phenotypes and ultimately how variation in ecological stressors can result in individual variation in the stress axis. To understand the evolutionary role of this programmed variation, we review recent work testing its adaptive function to predict how individual variation in stress-axis programming can scale up to influence populations and ecological communities. Throughout, we hope to emphasise that ecologists must understand the underlying mechanisms generating individual variation (*sensu* Williams 2008) to appreciate the ecological causes of

evolution (*sensu* MacColl 2011), especially within light of increasingly rapid human-induced alterations to ecosystems.

Ecological and environmental variation as maternal stressors

Numerous ecological stressors can affect maternal GCs and thus influence the programming of the offspring stress axis. Many of these extrinsic variables are those ecologists routinely study (e.g. predation risk, resource availability, social interactions), whereas some are novel emerging stressors (e.g. climatic variability and climate change, human disturbance). In studies of the ecological stressors that influence maternal GC levels, and therefore offspring, few researchers routinely measure GC levels from pre-breeding, pregnant or gravid females in free-living systems (Love *et al.* 2009). Moreover, prior studies linking GCs and reproduction focused almost exclusively on males (see Williams 2008). Traditionally therefore, less focus has been placed on maternal GCs during the stages when programming of the offspring stress axis is expected to occur. However, there are a number of emerging examples linking key ecological stressors to maternal GCs and offspring programming in a wide variety of free-living model systems.

PREDATION RISK AND RESOURCE AVAILABILITY

Two of the most significant environmental factors affecting organismal populations are predation and access to nutritional resources (Krebs *et al.* 1995; Clinchy *et al.* 2004; Sheriff, Krebs & Boonstra 2011). Ecologists have long theorised about the link between predation risk and physiological stress, and both risk and direct exposure elevate GCs in free-living vertebrates (rev. in Hawlena & Schmitz 2010; Clinchy, Sheriff & Zanette, *in press*). Predation risk has been shown to increase maternal GC levels in particular in a variety of free-living taxa. In mammals, an increase in the number of predators, or the risk of predation, has been demonstrated to increase maternal GC levels at both an individual and a population level (snowshoe hares – Boonstra *et al.* 1998; Sheriff, Krebs & Boonstra 2010, 2011; yellow-bellied marmots – Monclús, Tiulim & Blumstein 2011). In birds, an increase in nest predation, perceived risk of predation and direct exposure to predators have been shown to increase maternal GC levels, or GC secretion into eggs (barn swallows – Saino *et al.* 2005; European starlings – Love *et al.* 2008; song sparrows – Travers *et al.* 2010). In fish, an increase in the number of egg predators, or an experimental elevation in predation risk, increased both maternal GC levels and GC secretion into eggs (tropical damselfish – McCormick 1998; sticklebacks – Giesing *et al.* 2011).

Not surprisingly, the quantity, quality and predictability of resources can also act as ecological stressors in mothers (Love *et al.* 2005), given the significant role that GCs play in managing energetic balance at the level of the individual

(Landys, Ramenofsky & Wingfield 2006). Biologically relevant, unpredictable changes in food availability are known to increase maternal or female GC levels in both free-living birds and mammals (Kitaysky *et al.* 1999; Kitaysky, Piatt & Wingfield 2007; Benowitz-Fredericks, Shultz & Kitaysky 2008; Shultz & Kitaysky 2008; Jeanniard du Dot *et al.* 2009; Welcker *et al.* 2009), as do reductions in the energetic and micronutrient quality (rather than quantity) of resources (Chapman, Saj & Snaith 2007; Dantzer *et al.* 2011). A reduction in access to resources via competition can also reduce female quality and increase maternal GC levels (de Fraipont *et al.* 2000; Meylan *et al.* 2002). More often than not studies have linked the outcome of reduced resource quality/availability (i.e. low or declining body condition) to elevated maternal GC levels during egg laying or pregnancy (de Fraipont *et al.* 2000; Meylan *et al.* 2002; Love *et al.* 2005, 2009; Monclús, Tiulim & Blumstein 2011). Although less well understood, resource availability and predation risk can act synergistically to increase maternal GC levels (Sheriff, Krebs & Boonstra 2010), with interactive effects often being much stronger than predicted from studying their effects in isolation (Clinchy *et al.* 2004). Finally, reduced resources and declining maternal body condition can also affect post-natal maternal investment in offspring (i.e. reduced provisioning) via an increase in maternal GCs (Love *et al.* 2004; Angelier *et al.* 2007, 2009).

SOCIAL INTERACTION

Social interactions, conflicts and dominance relationships have long been known to act as environmental modulators of circulating GC levels in vertebrates (Sapolsky, Romero & Munck 2000; Creel 2001; Creel *et al.* *in press*). In social mammals, subordinate reproductive females often exhibit high GC levels compared to dominant reproductive females (Sapolsky, Romero & Munck 2000; Creel 2001). However, in cooperatively breeding mammals, dominant females generally have higher GC levels (Creel 2001; Koren, Mokady & Geffen 2008; although see Young *et al.* 2006). Furthermore, aggressive interactions, or even the perceived presence of increased competition via the visual presence of a conspecific, have been shown to increase maternal GCs, and therefore GCs deposited into the eggs, in tropical reef fish species (McCormick 1998, 1999, 2006). In free-ranging female morphs of the side-blotched lizard, individual, reproductive females exhibit different GC levels in relation to the dominance status of their nearest neighbour (Comendant *et al.* 2003). Finally, semi-colonial breeding female European starlings nesting away from conspecifics deposited increased levels of GCs into eggs compared to females nesting in close association with conspecifics (Love *et al.* 2008). Clearly, social interactions have the potential to influence maternal GC levels and offspring programming, and the adaptive advantages of such programming will greatly rely on the social structure and interactions between conspecifics.

HABITAT QUALITY, HUMAN DISTURBANCE AND CLIMATE CHANGE

Habitat degradation and increased human disturbance are predicted to increase circulating maternal GCs (Madliger & Love 2011). With respect to maternal stress, declining habitat quality has been shown to increase maternal GC levels in a variety of free-living taxa. Reductions in wintering habitat quality of migratory species can increase maternal GCs at arrival on breeding grounds (Marra & Holberton 1998) and large-scale geographic reductions, or variability in resource abundance/quality, can influence maternal GC levels during the pre-breeding stage (Kitaysky *et al.* 1999; Kitaysky, Piatt & Wingfield 2007; Shultz & Kitaysky 2008). Human disturbance, both recreational and industrial activity, can also cause an increase in maternal GCs in mammals (Creel *et al.* 2002; Wasser *et al.* 2011) and birds (Thiel *et al.* 2008; Zhang *et al.* 2011). Although relationships between habitat integrity and maternal GCs are often highly complex and may be mediated via effects on resource availability or other environmental factors (Madliger & Love 2011), a decline in habitat quality appears to be consistently related to elevated maternal GC levels.

Ecological physiologists have shown that variation in temperature, humidity and wind speed can all cause increases in stress-induced GCs in vertebrates, although the degree of this response can depend on resource availability and how well individuals are acclimated to conditions (Wingfield *et al.* 1998; Romero, Reed & Wingfield 2000; Breuner & Hahn 2003). However, current data linking climatic variation and GCs during the early stages of reproduction are heavily male-biased (Wingfield *et al.* 1998; Breuner & Hahn 2003). Sheriff *et al.* (2012) found that differences in the timing of snowmelt and spring conditions may alter seasonal patterns of GC secretion in free-living arctic ground squirrels, with later snowmelt potentially prolonging elevated GC levels in spring (Sheriff *et al.* 2012). Furthermore, unpredictably high precipitation and cooler temperatures were linked with elevated GC levels in these animals. Until recently, the effects of climate change on maternal GC levels were only explored theoretically (Boonstra 2004; Wingfield 2008). Thankfully, an increasing diversity of emerging work is proposing to examine the physiological mechanisms linking individuals to their environment (Love *et al.* 2010; Sheriff *et al.* 2012), and we expect studies linking climate change, maternal stress and offspring programming to increase in the coming years.

Mechanisms by which maternal stress can be transferred to offspring

Maternal stress results in life-long changes in stress axis function and behaviour in offspring across a large variety of taxa, and maternal GCs are the primary candidate mediating such programming (mammals – Meaney, Szyf & Seckl 2007; Sheriff, Krebs & Boonstra 2010; Monclús, Tiulim & Blumstein 2011; birds – Hayward & Wingfield 2004;

Saino *et al.* 2005; Love & Williams 2008b; fish – McCormick 1999, 2006; reptiles – de Fraipont *et al.* 2000; Meylan *et al.* 2002; Meylan & Clobert 2005). However, reproductive mode (placental vs. egg-laying) and the timing of maturation of the HPA axis relative to birth are important considerations in understanding the mechanisms by which maternal stress may program the offspring's brain.

In egg-laying vertebrates, embryos are exposed only to those maternal hormones deposited in the egg during the relatively short period when the yolk is being produced. Both experimental and predator-induced increases in maternal GCs during laying can increase GC concentration in the yolks and albumin of eggs (Hayward & Wingfield 2004; Love *et al.* 2005; Saino *et al.* 2005). Presently, little is known about the mechanisms of GC transfer between the mother and the egg (Groothuis *et al.* 2005), although there appears to be a positive correlation between maternal and yolk GC levels in at least two species (Love *et al.* 2005; Almasi *et al.* 2012). Changes in maternal care and provisioning in early life may also greatly affect stress axis function and behaviour in egg laying vertebrates. For example, in black-legged kittiwakes, a 20-day food restriction during development resulted in a subsequent increased GC levels in 30 day old chicks (Kitaysky *et al.* 1999). In European starlings, reducing maternal provisioning rates increased the responsiveness of the axis in offspring, especially female fledglings (Love & Williams 2008b).

In mammals, the timing of maturation of the HPA axis relative to birth is highly species specific, and in animals that give birth to precocial young (sheep, guinea pigs, hares) maximal brain growth and maturation takes place *in utero* (Dobbing & Sands 1979). In contrast, in animals that give birth to altricial young (rats, rabbits) much of the brain development occurs in the immediate postnatal period (Dobbing & Sands 1979). Thus, the timing of an increase in maternal stress will impact animals differentially depending upon the species involved. Evidence for the specific mechanisms of foetal and neonate programming comes from the biomedical, mammalian literature and is termed prenatal and postnatal programming and we will discuss as such.

PRENATAL PROGRAMMING

In laboratory mammalian studies, there is a large and growing body of research indicating that maternal stress during the later stages of gestation results in life-long changes in stress axis function and behaviour in offspring (Matthews *et al.* 2004; de Kloet *et al.* 2005; Owen, Andrews & Matthews 2005; Meaney, Szyf & Seckl 2007). GCs are essential for normal brain development, exerting a wide range of organisational effects via the glucocorticoid and mineralocorticoid receptors (GR and MR, respectively) in the brain (Matthews 1998). However, sustained exposure to, or removal of, GCs during development can permanently alter brain structure and function (Sapolsky 1987; Muneoka *et al.* 1997; Matthews 2002). Prenatal exposure to GCs causes a decrease in GR and MR in the

hippocampus, leading to a weaker negative feedback of the stress axis and elevated levels of GCs in adult offspring (Levitt *et al.* 1996; Welberg, Seckl & Holmes 2001; Welberg & Seckl 2001; Emack *et al.* 2008; Fig. 1).

Under normal conditions, exposure of the mammalian foetus to endogenous maternal GCs is restricted by placental expression of 11 β -hydroxysteroid dehydrogenase type 2 (11 β -HSD2; Burton & Waddell 1999; Seckl 2004). 11 β -HSD2 interconverts GCs (cortisol and corticosterone) to the inert forms cortisone and 11-dehydrocorticosterone (DH-B; Funder 1996). However, when mothers are exposed to a stressor, placental expression of 11 β -HSD2 decreases or fails to increase (Lesage *et al.* 2001; Lucassen *et al.* 2009) meaning that either offspring have little capacity to buffer their exposure, or that they do not respond because it is adaptive not to. Moreover, as maternal GC levels are much higher (10-fold in guinea pigs; Owen, Andrews & Matthews 2005) than those of the foetus, subtle changes in 11 β -HSD2 activity may have profound effects on foetal GC exposure.

The mechanisms by which foetal exposure to GCs alter brain development remain poorly understood. However, accumulating evidence points to altered epigenetic mechanisms, by which experiences 'program' long-term changes

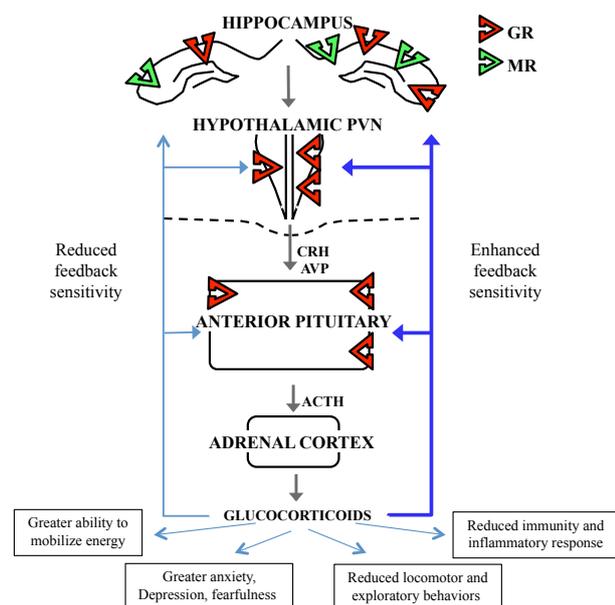


Fig. 1. The hypothalamic-pituitary-adrenal (HPA) axis and negative feedback response of Glucocorticoids (GCs). The sensitivity of the feedback response is due to the level of GCs and the number of GC and mineralcorticoid receptors (GR and MR, respectively) in the brain and GR in the body (de Kloet *et al.* 1998; Wingfield & Sapolsky 2003; Seckl 2004). High levels of maternal stress during gestation or altered maternal care (due to high levels of maternal stress) shortly after birth can programme the offspring brain, decreasing the number of receptors, reducing the feedback sensitivity and ultimately increasing offspring GC levels and associated behaviours (boxes; Welberg & Seckl 2001; Weaver *et al.* 2004; Abe *et al.* 2007; Meaney, Szyf & Seckl 2007; Emack *et al.* 2008; Sheriff, Krebs & Boonstra 2010). Figure adapted from Matthews 2002 & Boonstra 2004.

in gene expression in the absence of changes in DNA sequence (Szyf, McGowan & Meaney 2008; McGowan & Szyf 2010a,b). Laboratory experiments in rodents have shown that the physiological and behavioural alterations associated with prenatal stress are accompanied by transcriptional and epigenetic alterations in the brain in genes involved in HPA axis regulation, including altered DNA methylation in promoter regions of the GR and corticotrophin receptor genes (Mueller & Bale 2008). DNA methylation is the best-studied epigenetic marker, and its presence in gene promoters is usually associated with transcriptional silencing. Thus, prenatal programming effects derive from environmentally induced alterations of materno-foetal signalling, involving systems that determine foetal GC exposure. Ultimately, increased maternal adversity and GC levels result in an increase in foetal GC exposure and a permanent decrease in GR expression, which in turn leads to greater GCs levels in the offspring.

POSTNATAL PROGRAMMING

Maternal influences during the very early postnatal period can also effect GR expression and offspring behaviour (Francis & Meaney 1999; Meaney 2001; Meaney, Szyf & Seckl 2007). Evidence of postnatal programming dates back to studies by Levine and Denenberg during the 1950s who found that brief periods of neonate handling (as a proxy of greater maternal care) decrease offspring stress responses to stressors in mice and rats. More recently in rats, adult offspring of mothers who naturally exhibit high levels of care were found to show elevated hippocampal GR expression, enhanced negative feedback sensitivity and a more modest response to stressors (Liu *et al.* 1997; Fig. 1). As adults these offspring also display high maternal care themselves (Meaney 2001). Cross-fostering the biological offspring of high and low caring mothers on the first day of postnatal life reverses this phenotype (i.e. the offspring phenotype matches that of the mother that raised it, not its biological mother) suggesting a direct relationship between maternal care and the development of the HPA axis and behaviour (Francis *et al.* 1999).

Weaver and colleagues showed that maternal care altered DNA methylation in the offspring at a GR gene promoter in the hippocampus by inhibiting the binding of NGFI-A, a transcription factor that drives GR expression (Weaver *et al.* 2004, 2005, 2007; Fig. 2). In this case, the presence of DNA methylation at sites recognised by NGFI-A inhibited the binding of the transcription factor, leading to reduced mRNA expression. These results imply that increased DNA methylation of GR promoter leads to fewer GRs, a less rapid response to stress, and a slower recovery after the stressor is over. Sequences within the GR promoter showed lower levels of methylation in offspring of high caring mothers, while those sites in offspring of low caring mothers showed relatively higher levels of methylation. These differences emerged within the first week of life, were reversed with cross-fostering and

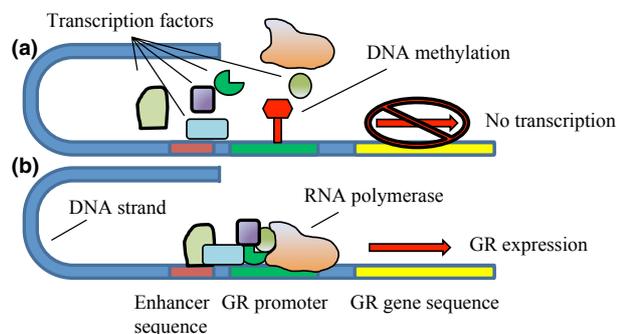


Fig. 2. (a) DNA methylation of glucocorticoid receptor (GR) promoter regions occurs in offspring of low licking and grooming mothers (decreased maternal care associated with high GC levels). High levels of DNA methylation of this promoter prevent transcription factor (NGFI-A) binding and greatly reduce GR expression. (b) However, in offspring of high licking and grooming mothers (increased maternal care associated with low GC levels) the GR promoter region shows lower levels of DNA methylation, associated with enhanced GR expression (Weaver *et al.* 2004, 2005, 2007; McGowan *et al.* 2011).

persisted into adulthood. Infusion with the histone deacetylase inhibitor Trichostatin A (leading to a relatively open chromatin configuration and generally increasing transcription) into the brain of low care offspring or infusion of methionine (a methyl donor which increases DNA methylation in the presence of methyltransferase enzymes) into the brain of high care offspring eliminated group differences in DNA methylation pattern, the binding of NGFIA to the GR promoter, GR expression and HPA responses to stressors. More recently, McGowan *et al.* (2011) found evidence of widespread, but specific, epigenetic and transcriptional alterations of the GR gene extending far beyond the GR promoter associated with differences in maternal care. A number of other groups have also found evidence of epigenetic regulation in the brain by altered parental care or stress-related early adversity (e.g. Murgatroyd *et al.* 2009; Roth *et al.* 2009). Thus, there is mounting evidence that epigenetic mechanisms coordinate wide spread changes in

gene expression in response to differences in early maternal care or adversity.

Postnatal programming effects derive from environmentally induced alterations of materno-neonatal interactions, involving systems that determine methylation patterns of GR gene promoter sequences and additional loci. Increased maternal care (resulting from mothers with lower GC levels) results in decreased methylation of the GR promoter and increased GR expression, which in turn leads to lower GC levels in adult offspring.

Programming of individual offspring phenotypes

Individual variation in the responsiveness of the stress axis is one of this system's hallmarks across a diversity of vertebrate taxa (see Breuner, Patterson & Hahn 2008), and yet we know very little about how this individual variation is mechanistically derived. Both inter-individual (i.e. differential exposure across mothers; Love *et al.* 2005, 2009; Sheriff, Krebs & Boonstra 2010) and intra-individual (i.e. differential exposure across offspring for a given mother; Love *et al.* 2008; Love & Williams 2008a) variation are expected to produce significant individual variation in the functioning of the stress axis of offspring. Sheriff, Krebs & Boonstra (2010) found that GC levels of pregnant snowshoe hares were directly echoed by that of their offspring, with entire litter groups reflecting the pattern of their mothers at the time the young were born (Fig. 3). Moreover, elevated maternal faecal GC levels correlated with a heightened responsiveness in their progeny to further stressors. These data are consistent with the idea that increased DNA methylation of the GR promoter, as result of maternal stress, decreases GR expression thus reducing negative feedback sensitivity to GCs, although this remains to be tested. Manipulative studies in birds also indicate that exposure to maternally derived GCs can contribute to variation in the stress reactivity of offspring (Hayward *et al.* 2006; Love & Williams 2008a,b). O. P. Love and T. D.

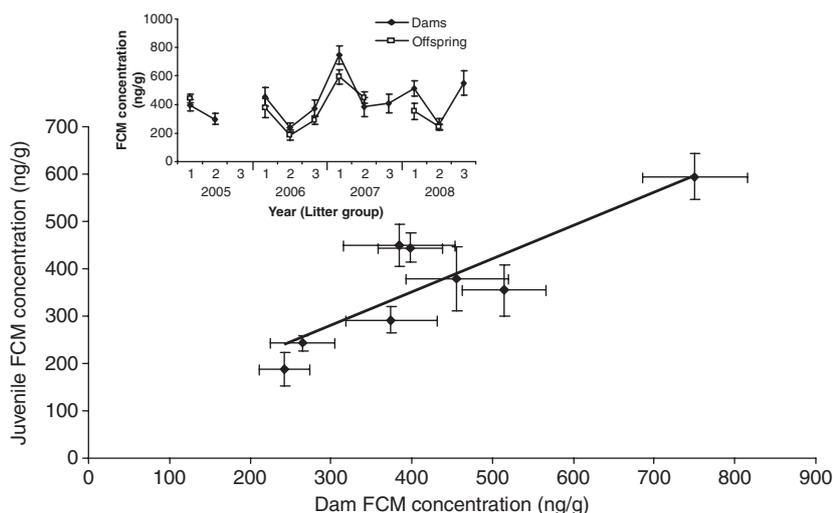


Fig. 3. Faecal cortisol metabolite (FCM) concentration (means \pm SE) in free-ranging snowshoe hare dams and juveniles ($r^2 = 0.73$, $P = 0.007$). Each point is the average from a different litter group (1–3) in 2005–2008. Juveniles were sampled within 1 week of weaning, 28 days after dams (i.e. juveniles are facing different conditions at the time of sampling than dams). Inset shows how juvenile FCM levels at weaning mirror that of dams at the time they gave birth (adapted from Sheriff, Krebs & Boonstra 2010).

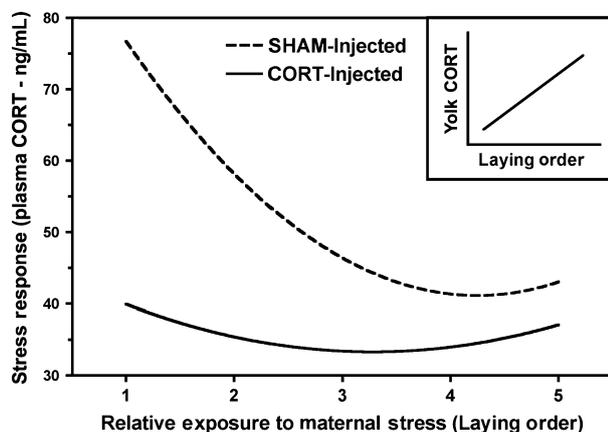


Fig. 4. Relative responsiveness of the stress axis in free-living European starling fledglings in relation to natural variation in exposure to maternal stress (changes in yolk corticosterone across laying order; see Love *et al.* 2008) and an experimental increase in maternal stress (CORT-injections of eggs); from O. P. Love & T. D. Williams (unpubl. data).

Williams (unpubl. data) found that inter-sibling variation in stress axis responsiveness was based on their differential exposure to maternal GCs: the sequential intra-clutch increases in maternal GC exposure experienced by individual offspring (i.e. intra-clutch variation in maternal GC exposure; Love *et al.* 2008) negatively correlated with the responsiveness of these offspring's stress axis (Fig. 4). Moreover, a further experimental (biologically relevant) increase in GC exposure further reduced the response of offspring, but only those exposed to the lowest initial maternal GC levels (O. P. Love & T. D. Williams, unpubl. data; Fig. 4). Laboratory experiments in rats have also shown that there is substantial within litter variation in maternal care, and that later in life (i.e. as mature adults) this difference is associated with differential behavioural responses in experiments measuring stress-related behaviours (van Hasselt *et al.* 2012). Therefore, despite siblings having a similar genetic and rearing environment, they may still face differential exposure to maternal GCs or maternal care, leading to variability in programming of the stress axis potentially due to differences in background GC levels or even receptor density/location during development. Unfortunately in free-living mammalian populations, although there is also much variation in HPA responsiveness within a litter (Sheriff, Krebs & Boonstra 2010), no study to date has investigated causality of birth order or uterine placement. Although more studies are necessary, maternal GC exposure likely plays key roles in maintaining variation in individual stress responses allowing organisms to adapt to present and future ecological stressors.

The evolutionary role of programmed phenotypes

Optimal functioning of the HPA axis has long been considered paramount to maximising fitness in vertebrates

(Wingfield *et al.* 1998; Boonstra 2004; Wingfield 2005; Romero, Dickens & Cyr 2009). Certainly, the vertebrate stress axis shows all the potential features of an adaptive trait: large intra-specific (individual) variation (Williams 2008); repeatability under consistent conditions (Ouyang, Hau & Bonier 2011); heritability (Bartels *et al.* 2003; Fedorenko *et al.* 2004; Evans *et al.* 2006; Solberg *et al.* 2006) and is responsive to selection in captivity (Satterlee & Johnson 1988; Evans *et al.* 2006). Indeed, a number of studies have shown that variation in the responsiveness of the stress axis is adaptive when individuals are faced with changes in their ecological surroundings (i.e. Wingfield & Hunt 2002; Breuner & Hahn 2003). We also know that individuals with lower responses tend to be less affected by disturbance and show reduced rates of reproductive abandonment (Silverin 1998; Holberton & Wingfield 2003; Love *et al.* 2004; Angelier *et al.* 2009). Moreover, variation in HPA axis responsiveness in offspring (Cavigelli & McClintock 2003; Blas *et al.* 2007) and adults (Angelier, Holberton & Marra 2010) has been correlated in some cases with survival in vertebrates (Breuner, Patterson & Hahn 2008). Finally, experimental manipulations of maternal stress are known to alter HPA axis functioning of exposed offspring in a number of non-biomedical systems (Hayward *et al.* 2006; Love & Williams 2008b; Sheriff, Krebs & Boonstra 2010; Haussmann *et al.* 2012). However, how much information exists directly linking maternal programming of the stress axis with the fitness (reproductive success and survival) of offspring?

We generally lack data on how the programming of HPA activity *directly* affects offspring fitness in free-living species as few studies have performed manipulations of maternal GC exposure and then followed offspring into adulthood. However, data from studies of reproductive output in mothers, immediate (developmental) survival of offspring and proxies of fitness (growth, body size) allow for some predictions. Programming by maternal GCs is expected to influence offspring fitness through complex trade-offs between investment in development, reproduction and survival. Not surprisingly then, exposure to maternal GCs results in decreases in initial offspring body size and weight during early development and lower reproductive output for mothers of free-living species (Love *et al.* 2005; Meylan & Clobert 2005; Saino *et al.* 2005; Love & Williams 2008a; Sheriff, Krebs & Boonstra 2009, 2010). However, a stress-induced reduction in initial maternal investment and overall output can benefit remaining offspring in the longer term through a reduction in developmental competition (Love *et al.* 2005; Breuner 2008; Love & Williams 2008a), as well as beneficially influencing both dispersal (de Fraipont *et al.* 2000; Meylan *et al.* 2002) and anti-predator behaviour in offspring (Meylan & Clobert 2005; Uller & Olsson 2006; Chin *et al.* 2009; Giesing *et al.* 2011).

Recently, maternal programming has been proposed to act as an adaptive bridge between the maternal and offspring environment (Love *et al.* 2005; Love & Williams

2008a; Sheriff, Krebs & Boonstra 2009, 2010; work by Love and colleagues reviewed in Breuner 2008). To appreciate both the potential influence and direction of this relationship, it is critically important to examine phenotypic adjustments within the immediate environmental context in which they occur, as well as the longer-term environmental context that offspring face as reproductive adults (Love *et al.* 2005; Love & Williams 2008a; Sheriff, Krebs & Boonstra 2009, 2010). In circumstances when maternal signalling is a reliable predictor of the offspring's future environment, maternal programming may indeed be an adaptive mechanism, increasing offspring and even maternal fitness (Love *et al.* 2005; Love & Williams 2008a; Chin *et al.* 2009). This paradigm has recently been defined as the 'Maternal-Match Hypothesis' (Love *et al.* 2005; Love & Williams 2008a; work by Love and colleagues reviewed in Breuner 2008), which would be a refinement of a broader 'Environmental-Match Hypothesis' where offspring attempt to use cues to match their phenotypes to their expected future environments. Conversely, if maternal signalling acts as a poor predictor of an offspring's future environment, maternal programming could in fact be maladaptive, negatively affecting offspring fitness (Sheriff, Krebs & Boonstra 2009, 2010). Indeed, theoretical work on maternal effects has suggested that similarities between parents and offspring (and even grandparents and grand-offspring) induced via maternal effects could cause a significant temporal lag in the phenotype-environment relationship (Kirkpatrick & Lande 1989). The result would be a mismatch between an offspring's phenotype and its expected future environment, which could in theory lead to effects on population cycles and ultimately communities. As such, as the evolutionary trajectory of maternal programming effects at the individual level are highly context specific, their consequences for offspring therefore have different potential ramifications for how individual responses scale up to influence populations and communities.

Scaling maternal programming up to populations and communities

Although acting at the level of the individual, maternal programming has the potential to greatly influence population dynamics by acting on factors such as reproduction, survival and dispersal. For example, maternal programming is known to play a large role in snowshoe hare population cycling (Sheriff, Krebs & Boonstra 2009, 2010, 2011). During the decline phase, the high risk of predation increases maternal GCs and reduces litter size, and offspring birth weight and size, while increasing offspring's baseline GC levels and stress responses. These effects persist into adulthood, likely lowering adult-offspring reproduction. The lower reproductive output would decrease the time necessary for foraging and thus may increase maternal survival (and thus maternal and offspring fitness). The increase in offspring GCs (and anti-predator behaviours associated with prenatally elevated GC levels; Emack

et al. 2008) may increase offspring survival. Thus, during the decline phase although maternal programming may decrease reproduction it would result in higher maternal and offspring survival; potentially allowing some individuals to escape the overwhelmingly negative predation effects to survive the collapse of the population. At the end of the decline phase and beginning of the low phase (where mothers experience high predation risk while offspring do not) the trade-off between a decrease in reproduction and an increase in anti-predator behaviours would be very costly. Thus, maternal programming can significantly influence population dynamics depending upon the balance between the negative impact on reproduction and the positive effect on survival in an environmentally context dependent manner.

Maternal programming of an offspring's stress axis can also affect its propensity to disperse, although dispersal decisions may be the result of a complex interplay between maternal GC levels and maternal body condition (de Fraipont *et al.* 2000; Meylan *et al.* 2002; Meylan & Clobert 2005). For example in common lizards, Meylan *et al.* (2002) found that increased maternal GCs decreased dispersal in those offspring born to corpulent mothers. High maternal GCs in less corpulent mothers resulted in increased offspring dispersal. In other species, plasma GC levels in juveniles have also been found to affect dispersal (Wingfield 1994; Silverin 1997). In willow tits, experimentally increased GC levels enhanced dispersal rates; however, similar to lizards this was context-dependent. GCs only increased dispersal during a period of flock establishment (July–September); however, when permanent winter flocks had become established, increased GC levels had no effect on dispersal. Thus, maternal programming may influence dispersal-mediated effects on populations in a highly context-dependent manner.

At a community level, maternal programming may impact ecosystem dynamics by changing energy and material flow within and between trophic levels (Hawlena & Schmitz 2010). Elevated maternal GCs result in greater offspring GCs, which affects metabolic rate and digestive processes, and increases gluconeogenesis (Wingfield *et al.* 1998; Sapolsky, Romero & Munck 2000). Higher metabolism leads to greater energy expenditure at rest, and animals will compensate for higher maintenance costs by increasing foraging quantity or by foraging on higher quality prey. This is exacerbated by the fact that increased GCs reduce digestive efficiency and energy intake, thus reducing conversion efficiency of assimilated nutrients into body tissues. Pre-programmed offspring with higher GC levels also have greater gluconeogenesis, which leads to increased breakdown of proteins to produce glucose, and can substantially change body-nutrient composition, reducing N-rich proteins (Sterner & Ellser 2002). Gluconeogenesis may also increase N-excretion and, because proteins (amino acids) are the major N-containing molecule, this will increase body C:N ratio (Sterner & Ellser 2002). Thus, offspring will have reduced energy stores to fuel greater

energy demands and likely forage preferentially on higher quality prey. However, they may also have an altered body-nutrient composition leading to impaired growth, development and body condition reducing competitive ability within a trophic level and their overall value to upper level predators. With energy flow reduced by 90% between trophic levels even small changes in energy flow through one trophic level may have severe consequences for the ecosystem as a whole. The emerging generality is that maternal programming has context dependent effects on offspring phenotypes that may have cascading effects at the ecosystem level.

As this review has noted, there exists many parallels between ecological and laboratory systems which can serve to foster both collaborations and inspiration for further integration focusing on the strengths inherent in each approach. From a proximate standpoint, it remains critical to test hypotheses about underlying molecular and epigenetic mechanisms derived from laboratory studies in natural populations, where the timing, intensity and ecological relevance of manipulations early in life may have distinct consequences. From an ultimate standpoint, for ecologically based studies of maternal stress programming to increase their academic relevance they must strive to fundamentally link proximate phenotypic effects with offspring and maternal fitness.

Acknowledgements

The authors wish to thank R. Boonstra for both the opportunity to write this review and for his positive feedback, as well as C. Fox and an anonymous reviewer for further comments that improved this work. O.P.L. is supported by an operating grant from the National Science and Engineering Research Council (NSERC) of Canada. M.J.S. is supported by NSERC and International Polar Year (IPY) post-doctoral fellowships. P.O.M. is supported by NSERC, the Connaught Fund and the CFIDS Association of America.

References

Abe, H., Hidaka, N., Kawagoe, C., Odagiri, K., Watanabe, Y., Ikeda, T., Ishizuka, Y., Hashiguchi, H., Takeda, R., Nishimori, T. & Ishida, Y. (2007) Prenatal psychological stress causes higher emotionality, depression-like behavior, and elevated activity in the hypothalamo-pituitary-adrenal axis. *Neuroscience Research*, **59**, 145–151.

Almasi, B., Rettenbacher, S., Müeller, C., Brill, S., Wagner, H. & Jenni, L. (2012) Maternal corticosterone is transferred into the egg yolk. *General and Comparative Endocrinology*, **178**, 139–144.

Angelier, F., Holberton, R.L. & Marra, P.P. (2010) Does stress response predict return rate in a migratory bird species? A study of American redstarts and their non-breeding habitat. *Proceedings of the Royal Society B*, **276**, 3545–3551.

Angelier, F., Shaffer, S.A., Weimerskirch, H., Trouvé, C. & Chastel, O. (2007) Corticosterone and foraging behavior in a pelagic seabird. *Physiological and Biochemical Zoology*, **80**, 283–292.

Angelier, F., Clément-Chastel, C., Welcker, J., Gabrielsen, G.W. & Chastel, O. (2009) How does corticosterone affect parental behavior and reproductive success? A study of prolactin in black-legged kittiwakes. *Functional Ecology*, **23**, 784–793.

Bartels, M., Van den Berg, M., Sluyter, F., Boomsma, D.I. & de Geus, E.J.C. (2003) Heritability of cortisol levels: review and simultaneous analysis of twin studies. *Psychoneuroendocrinology*, **28**, 121–137.

Benowitz-Fredericks, Z.M., Shultz, M.T. & Kitaysky, A.S. (2008) Stress hormones suggest opposite trends of food availability for planktivorous and piscivorous seabirds in 2 years. *Deep Sea Research II*, **55**, 1868–1876.

Blas, J., Bortolotti, G.R., Tella, J.L., Baos, R. & Marchant, T.A. (2007) Stress response during development predicts fitness in a wild, long lived vertebrate. *Proceedings of the National Academy of Sciences of the United States of America*, **104**, 8880–8884.

Bonier, F., Martin, P.R., Moore, I.T. & Wingfield, J.C. (2009) Do baseline glucocorticoids predict fitness? *Trends in Ecology and Evolution*, **24**, 634–642.

Boonstra, R. (2004) Coping with changing northern environments: the role of the stress axis in birds and mammals. *Integrative and Comparative Biology*, **44**, 95–108.

Boonstra, R. (2005) Equipped for life: the adaptive role of the stress axis in male mammals. *Journal of Mammalogy*, **86**, 236–247.

Boonstra, R., Hik, D., Singleton, G.R. & Tinnikov, A. (1998) The impact of predator-induced stress on the snowshoe hare cycle. *Ecological Monographs*, **68**, 371–394.

Breuner, C.W. (2008) Maternal stress, glucocorticoids, and the maternal/fetal match hypothesis. *Hormones and Behavior*, **54**, 485–487.

Breuner, C.W. & Hahn, T.P. (2003) Integrating stress physiology, environmental change, and behavior in free-living sparrows. *Hormones and Behavior*, **43**, 115–123.

Breuner, C.W., Patterson, S.H. & Hahn, T.P. (2008) In search of relationship between the acute adrenocortical response and fitness. *General and Comparative Endocrinology*, **157**, 288–295.

Burton, P.J. & Waddell, B.J. (1999) Dual function of 11 β -hydroxysteroid dehydrogenase in placental: modulating placental glucocorticoid passage and local steroid action. *Biological Reproduction*, **60**, 234–240.

Cavigelli, S.A. & McClintock, M.K. (2003) Fear of novelty in infant rats predicts adult corticosterone dynamics and an early death. *Proceedings of the National Academy of Sciences of the United States of America*, **100**, 16131–16136.

Chapman, C.A., Saj, T.L. & Snaith, T.V. (2007) Temporal dynamics of nutrition, parasitism, and stress in colobus monkeys: implications for population regulation and conservation. *American Journal of Physical Anthropology*, **134**, 240–250.

Chin, E.H., Love, O.P., Verspoor, J.J., Williams, T.D., Rowley, K. & Burness, G. (2009) Juveniles exposed to embryonic corticosterone have enhanced flight performance. *Proceedings of the Royal Society B*, **276**, 499–505.

Clinchy, M., Sheriff, M.J. & Zanette, L. (in press) Ecological processes and the ecology of stress: the demographic impact of predator-induced fear and stress. *Functional Ecology*.

Clinchy, M., Zanette, L., Boonstra, R., Wingfield, J.C. & Smith, J.N.M. (2004) Balancing food and predator pressure induces chronic stress in songbirds. *Proceedings of the Royal Society of London B*, **271**, 2473–2479.

Comendant, T., Sinervo, B., Svensson, E.I. & Wingfield, J. (2003) Social competition, corticosterone and survival in female lizard morphs. *Journal of Evolutionary Biology*, **16**, 948–955.

Creel, S. (2001) Social dominance and stress hormones. *Trends in Ecology and Evolution*, **16**, 491–497.

Creel, S., Fox, J.E., Hardy, A., Sands, J., Garrot, B. & Peterson, R.O. (2002) Snowmobile activity and glucocorticoid stress responses in wolves and elk. *Conservation Biology*, **16**, 809–814.

Creel, S., Dantzer, B., Goymann, W. & Rubenstein, D.R. (in press) Ecological processes and the ecology of stress: the impact of the social environment. *Functional Ecology*.

Dantzer, B., McAdam, A.G., Palme, R., Boutin, S. & Boonstra, R. (2011) How does diet affect fecal steroid hormone metabolite concentrations? An experimental examination in red squirrels. *General and Comparative Endocrinology*, **174**, 124–131.

Dobbing, J. & Sands, J. (1979) Comparative aspects of the brain growth spurt. *Early Human Development*, **3**, 79–83.

Emack, J., Kostaki, A., Walker, C.-D. & Matthews, S.G. (2008) Chronic maternal stress affects growth, behavior and hypothalamo-pituitary-adrenal function in juvenile offspring. *Hormones and Behavior*, **54**, 514–520.

Evans, M.R., Roberts, M.L., Buchanan, K.L. & Goldsmith, A.R. (2006) Heritability of corticosterone response and changes in life history traits during selection in the zebra finch. *Journal of Evolutionary Biology*, **19**, 343–352.

Federenko, I.S., Nagamine, M., Hellhammer, D.H., Wadhwa, P.D. & Wust, S. (2004) The heritability of hypothalamus pituitary adrenal axis responses to psychosocial stress is context dependent. *Journal of Clinical Endocrinology and Metabolism*, **89**, 6244–6250.

de Fraipont, M., Clobert, J., John-Alder, H. & Meylan, S. (2000) Increased pre-natal maternal corticosterone promotes philopatry of

- offspring in common lizard *Lacerta vivipara*. *Journal of Animal Ecology*, **69**, 404–413.
- Francis, D.D. & Meaney, M.J. (1999) Maternal care and the development of stress responses. *Current Opinion in Neurobiology*, **9**, 128–134.
- Francis, D., Diorio, J., Liu, D. & Meaney, M.J. (1999) Nongenomic transmission across generations of maternal behavior and stress responses in the rat. *Science*, **286**, 1155–1158.
- Funder, J.W. (1996) 11 β -Hydroxysteroid dehydrogenase: new answers, new questions. *European Journal of Endocrinology*, **134**, 267–268.
- Giesing, E.R., Suski, C.D., Warner, R.E. & Bell, A.M. (2011) Female sticklebacks transfer information via eggs: effects of maternal experience with predators on offspring. *Proceedings of the Royal Society B*, **278**, 1753–1759.
- Gluckman, P.D., Hanson, M.A. & Spencer, H.G. (2005a) Predictive adaptive responses and human evolution. *Trends in Ecology and Evolution*, **20**, 527–533.
- Gluckman, P.D., Hanson, M.A., Spencer, H.G. & Bateson, P. (2005b) Environmental influences during development and their later consequences for health and disease: implications for the interpretation of empirical studies. *Proceedings of the Royal Society of London B*, **272**, 671–677.
- Groothuis, T.G.G., Müller, W., von Engelhardt, N., Carere, C. & Eising, C. (2005) Maternal hormones as a tool to adjust offspring phenotype in avian species. *Neuroscience and Biobehavioral Reviews*, **29**, 329–352.
- Hadany, L., Beker, T., Eshel, I. & Feldman, M. (2006) Why is stress so deadly? An evolutionary perspective. *Proceedings of the Royal Society B*, **273**, 881–885.
- Hales, C.N. & Barker, D.J. (1992) Type 2 (non-insulin-dependent) diabetes mellitus: the thrifty phenotype hypothesis. *Diabetologia*, **35**, 595–601.
- van Hasselt, F.N., Tieskens, J.M., Trezza, V., Krugers, H.J., Vanderschuren, L.J. & Joëls, M. (2012) Within-litter variation in maternal care received by individual pups correlates with adolescent social play behavior in male rats. *Physiology and Behavior*, **106**, 701–706.
- Hausmann, M.F., Longenecker, A.S., Marchetto, N.M., Juliano, S.A. & Bowden, R.M. (2012) Embryonic exposure to corticosterone modifies the juvenile stress response, oxidative stress and telomere length. *Proceedings of the Royal Society B*, **279**, 1447–1456.
- Hawlena, D. & Schmitz, O.J. (2010) Physiological stress as a fundamental mechanism linking predation to ecosystem functioning. *American Naturalist*, **175**, 537–556.
- Hayward, L.S. & Wingfield, J.C. (2004) Maternal corticosterone is transferred to avian yolk and may alter offspring growth and adult phenotype. *General and Comparative Endocrinology*, **135**, 365–371.
- Hayward, L.S., Richardson, J.B., Grogan, M.N. & Wingfield, J.C. (2006) Sex differences in the organizational effects of corticosterone in the egg yolk of quail. *General and Comparative Endocrinology*, **146**, 144–148.
- Holberton, R.L. & Wingfield, J.C. (2003) Modulating the corticosterone stress response: a mechanism for balancing individual risk and reproductive success in arctic-breeding sparrows? *Auk*, **120**, 1140–1150.
- Jeanniard du Dot, T., Rosen, D.A.S., Richmond, J.P., Kitaysky, A.S., Zinn, S.A. & Trites, A.W. (2009) Changes in glucocorticoids, IGF-I and thyroid hormones as indicators of nutritional stress and subsequent re-feeding in Steller sea lions (*Eumetopias jubatus*). *Comparative Biochemistry and Physiology A*, **152**, 524–534.
- Kirkpatrick, M. & Lande, R. (1989) The evolution of maternal characteristics. *Evolution*, **43**, 485–503.
- Kitaysky, A.S., Piatt, J.F. & Wingfield, J.C. (2007) Stress hormones link food availability and population processes in seabirds. *Marine Ecology Progress Series*, **352**, 245–258.
- Kitaysky, A.S., Piatt, J.F., Wingfield, J.C. & Romano, M. (1999) The adrenocortical stress-response of black-legged kittiwake chicks in relation to dietary restrictions. *Journal of Comparative Physiology B*, **169**, 303–310.
- de Kloet, E.R., Vreugdenhil, E., Oitzl, M.S. & Joels, M. (1998) Brain corticosteroid receptor balance in health and disease. *Endocrine Review*, **19**, 269–301.
- de Kloet, R.E., Sibug, R.M., Helmerhorst, F.M. & Schmidt, M. (2005) Stress, genes and the mechanism of programming the brain for later life. *Neuroscience and Biobehavioral Reviews*, **29**, 271–281.
- Koren, L., Mokady, O. & Geffen, E. (2008) Social status and cortisol levels in singing rock hyraxes. *Hormones and Behavior*, **54**, 212–216.
- Krebs, C.J., Boutin, S., Boonstra, R., Sinclair, A.R.E., Smith, J.N.M., Dale, M.R.T., Martin, K. & Turkington, R. (1995) Impact of food and predation on the snowshoe hare cycle. *Science*, **269**, 1112–1115.
- Landys, M., Goymann, W. & Slagsvold, T. (2011) Rearing conditions have long-term consequences for stress responsiveness in free-living great tits. *General and Comparative Endocrinology*, **174**, 219–224.
- Landys, M.M., Ramenofsky, M. & Wingfield, J.C. (2006) Actions of glucocorticoids at a seasonal baseline as compared to stress-related levels in the regulation of periodic life processes. *General and Comparative Endocrinology*, **148**, 132–149.
- Lendvai, A.Z., Loiseau, C., Sorci, G. & Chastel, O. (2009) Early developmental conditions affect stress response in juvenile but not in adult house sparrows (*Passer domesticus*). *General and Comparative Endocrinology*, **160**, 30–35.
- Lesage, J., Blondeau, B., Grino, M., Breant, B. & Dupouy, J.P. (2001) Maternal undernutrition during late gestation induces fetal overexposure to glucocorticoids and intrauterine growth retardation, and disturbs the hypothalamo-pituitary-adrenal axis in the newborn rat. *Endocrinology*, **142**, 1692–1702.
- Levitt, N.S., Lindsay, R.S., Holmes, M.C. & Seckl, J.R. (1996) Dexamethasone in the last week of pregnancy attenuates hippocampal glucocorticoid receptor gene expression and elevates blood pressure in the adult offspring in the rat. *Neuroendocrinology*, **64**, 412–418.
- Liu, D., Diorio, J., Tannenbaum, B., Caldji, C., Francis, D., Freedman, A., Sharma, S., Pearson, D., Plotsky, P.M. & Meaney, M.J. (1997) Maternal care, hippocampal glucocorticoid receptors, and hypothalamo-pituitary-adrenal responses to stress. *Science*, **277**, 1659–1662.
- Love, O.P., Bird, D.M. & Shutt, L.J. (2003) Plasma corticosterone in American kestrel siblings: effects of age, hatching order, and hatching asynchrony. *Hormones and Behavior*, **43**, 480–488.
- Love, O.P. & Williams, T.D. (2008a) The adaptive value of stress-induced phenotypes: effects of maternally derived corticosterone on sex-biased investment, cost of reproduction, and maternal fitness. *American Naturalist*, **172**, E135–E149.
- Love, O.P. & Williams, T.D. (2008b) Plasticity in the adrenocortical response of a free-living vertebrate: the role of pre- and post-natal developmental stress. *Hormones and Behavior*, **54**, 496–505.
- Love, O.P., Breuner, C.W., Vézina, F. & Williams, T.D. (2004) Mediation of a corticosterone-induced reproductive conflict. *Hormones and Behavior*, **46**, 59–65.
- Love, O.P., Chin, E.H., Wynne-Edwards, K.E. & Williams, T.D. (2005) Stress hormones: a link between maternal condition and sex-biased reproductive investment. *American Naturalist*, **166**, 751–766.
- Love, O.P., Wynne-Edwards, K.E., Bond, L. & Williams, T.D. (2008) Determinants of within- and among-clutch variation of yolk corticosterone in the European starling. *Hormones and Behavior*, **53**, 104–111.
- Love, O.P., Gilchrist, H.G., Bêty, J., Wynne-Edwards, K.E., Berzins, L. & Williams, T.D. (2009) Using life-histories to predict and interpret variability in yolk hormones. *General and Comparative Endocrinology*, **163**, 169–174.
- Love, O.P., Gilchrist, H.G., Descamps, S., Semeniuk, C.A.D. & Bêty, J. (2010) Pre-laying climatic cues can time reproduction to optimally match offspring hatching and ice conditions in an Arctic marine bird. *Oecologia*, **164**, 277–286.
- Low, F.M., Gluckman, P.D. & Hanson, M.A. (2012) Developmental plasticity, epigenetics and human health. *Evolutionary Biology*, DOI: 10.1007/s11692-011-9157-0
- Lucassen, P.J., Bosch, O.J., Jousma, E., Krumer, S.A., Andrew, R., Seckl, J.R. & Neumann, I.D. (2009) Prenatal stress reduces postnatal neurogenesis in rats selectively bred for high, but not low, anxiety: possible key role of placental 11 β -hydroxysteroid dehydrogenase type 2. *European Journal of Neuroscience*, **29**, 97–103.
- MacColl, A.D.C. (2011) The ecological causes of evolution. *Trends in Ecology and Evolution*, **26**, 514–522.
- Macri, S. & Wu, H. (2006) Developmental plasticity of HPA and fear responses in rats: a critical review of the maternal mediation hypothesis. *Hormones and Behavior*, **50**, 667–680.
- Madliger, C. & Love, O.P. 2011. Links between baseline stress physiology, habitat quality, and fitness in an aerial insectivore. *Frontiers in Endocrinology Conference Abstract: NASCE 2011: The inaugural meeting of the North American Society for Comparative Endocrinology*.
- Marra, P.P. & Holberton, R.L. (1998) Corticosterone levels as indicators of habitat quality: effects of habitat segregation in a migratory bird during the non-breeding season. *Oecologia*, **116**, 284–292.
- Matthews, S.G. (1998) Dynamic changes in glucocorticoid and mineralocorticoid receptor mRNA in the developing guinea pig brain. *Developmental Brain Research*, **107**, 123–132.
- Matthews, S.G. (2002) Early programming of the hypothalamo-pituitary-adrenal axis. *Trends in Endocrinology and Metabolism*, **13**, 373–380.
- Matthews, S.G., Owen, D., Kalabis, G., Banjanin, S., Setiawan, E.B., Dunn, E.A. & Andrews, M.H. (2004) Fetal glucocorticoid exposure and

- hypothalamo-pituitary-adrenal (HPA) function after birth. *Endocrine Research*, **30**, 827–836.
- McCormick, M.I. (1998) Behaviorally induced maternal stress in a fish influences progeny quality by a hormonal mechanism. *Ecology*, **79**, 1873–1883.
- McCormick, M.I. (1999) Experimental test of the effect of maternal hormones on larval quality of a coral reef fish. *Oecologia*, **118**, 412–422.
- McCormick, M.I. (2006) Mothers matter: crowding leads to stressed mothers and smaller offspring in marine fish. *Ecology*, **87**, 1104–1109.
- McGowan, P.O. & Szyf, M. (2010a) Environmental epigenomics: understanding the effects of parental care on the epigenome. *Essays in Biochemistry*, **48**, 275–287.
- McGowan, P.O. & Szyf, M. (2010b) The epigenetics of social adversity in early life: implications for mental health outcomes. *Neurobiology of Disease*, **39**, 66–72.
- McGowan, P.O., Sasaki, A., Huang, T.C., Unterberger, A., Suderman, M., Ernst, C., Meaney, M.J., Turecki, G. & Szyf, M. (2008) Promoter-wide hypermethylation of the ribosomal RNA gene promoter in the suicide brain. *PLoS ONE*, **3**, e2085.
- McGowan, P.O., Sasaki, A., D'Alessio, A.C., Dymov, S., Labonté, B., Szyf, M., Turecki, G. & Meaney, M.J. (2009) Epigenetic regulation of the glucocorticoid receptor in human brain associates with childhood abuse. *Nature Neuroscience*, **12**, 342–348.
- McGowan, P.O., Suderman, M., Sasaki, A., Huang, T.C., Hallett, M., Meaney, M.J. & Szyf, M. (2011) Broad epigenetic signature of maternal care in the brain of adult rats. *PLoS ONE*, **6**, e14739.
- Meaney, M.J. (2001) Maternal care, gene expression, and the transmission of individual differences in stress reactivity across generations. *Annual Review of Neuroscience*, **24**, 1161–1192.
- Meaney, M., Szyf, M. & Seckl, J.R. (2007) Epigenetic mechanisms of perinatal programming of hypothalamic-pituitary-adrenal function and health. *Trends in Molecular Medicine*, **13**, 269–277.
- Meylan, S. & Clobert, J. (2005) Is corticosterone-mediated phenotype development adaptive? Maternal corticosterone treatment enhances survival in male lizards *Hormones and Behavior*, **48**, 44–52.
- Meylan, S., Belliure, J., Clobert, J. & de Fraipont, M. (2002) Stress and body condition as prenatal and postnatal determinants of dispersal in the common lizard (*Lacerta vivipara*). *Hormones and Behavior*, **42**, 319–326.
- Monclús, R., Tiulim, J. & Blumstein, D.T. (2011) Older mothers follow conservative strategies under predator pressure: the adaptive role of maternal glucocorticoids in yellow-bellied marmots. *Hormones and Behavior*, **60**, 660–665.
- Mueller, B.R. & Bale, T.L. (2008) Sex-specific programming of offspring emotionality after stress early in pregnancy. *Journal of Neuroscience*, **28**, 9055–9065.
- Muneoka, K., Mikuni, M., Ogawa, T., Kitera, K., Kamei, K., Takigawa, M. & Takahashi, K. (1997) Prenatal dexamethasone exposure alters brain monoamine metabolism and adrenocortical response in rat offspring. *American Journal of Physiology-Regulatory, Integrative, and Comparative Physiology*, **273**, 1669–1675.
- Murgatroyd, C., Patchev, A.V., Wu, Y., Micale, V., Bockmühl, Y., Fischer, D., Holsboer, F., Wotjak, C.T., Almeida, O.F. & Spengler, D. (2009) Dynamic DNA methylation programs persistent adverse effects of early-life stress. *Nature Neuroscience*, **12**, 1559–1566.
- Ouyang, J.Q., Hau, M. & Bonier, F. (2011) Within seasons and among years: when are corticosterone levels repeatable? *Hormones and Behavior*, **60**, 559–564.
- Owen, D., Andrews, M.H. & Matthews, S.G. (2005) Maternal adversity, glucocorticoids and programming of neuroendocrine function and behaviour. *Neuroscience and Biobehavioral Reviews*, **29**, 209–226.
- Pravosudov, V.V. & Kitaysky, A.S. (2006) Effects of nutritional restrictions during post-hatching development on adrenocortical function in western scrub-jays (*Aphelocoma californica*). *General and Comparative Endocrinology*, **145**, 25–31.
- Preisser, E.L. (2009) The physiology of predator stress in free-ranging prey. *Journal of Animal Ecology*, **78**, 1103–1105.
- Reeder, D.M. & Kramer, K.M. (2005) Stress in free-ranging mammals: integrating physiology, ecology, and natural history. *Journal of Mammalogy*, **86**, 225–235.
- Romero, L.M., Dickens, M.J. & Cyr, N.E. (2009) The reactive scope model – a new model integrating homeostasis, allostasis, and stress. *Hormones and Behavior*, **55**, 375–389.
- Romero, L.M., Reed, M. & Wingfield, J.C. (2000) Effects of weather on corticosterone responses in wild free-living passerine birds. *General and Comparative Endocrinology*, **118**, 113–122.
- Roth, T.L., Lubin, F.D., Funk, A.J. & Sweatt, J.D. (2009) Lasting epigenetic influence of early-life adversity on the BDNF gene. *Biological Psychiatry*, **65**, 760–769.
- Saino, N., Romano, M., Ferrari, R.P., Martinelli, R. & Möller, A.P. (2005) Stressed mothers lay eggs with high corticosterone levels which produce low-quality offspring. *Journal of Experimental Zoology*, **303A**, 998–1006.
- Sapolsky, R.M. (1987) Glucocorticoids and hippocampal damage. *Trends in Neuroscience*, **10**, 346–349.
- Sapolsky, R.M., Romero, L.M. & Munck, A.U. (2000) How do glucocorticoids influence stress responses? Integrating permissive, suppressive, stimulatory, and preparative actions. *Endocrine Reviews*, **21**, 55–89.
- Satterlee, D.G. & Johnson, W.A. (1988) Selection of Japanese quail for contrasting blood corticosterone response to immobilization. *Poultry Science*, **67**, 25–32.
- Seckl, J.R. (2001) Glucocorticoid programming of the fetus; adult phenotypes and molecular mechanisms. *Molecular and Cellular Endocrinology*, **185**, 61–71.
- Seckl, J.R. (2004) Prenatal glucocorticoids and long-term programming. *European Journal of Endocrinology*, **151**, U49–U62.
- Seckl, J.R. & Meaney, M.J. (2004) Glucocorticoid programming. *Annals of the New York Academy of Science*, **1032**, 63–84.
- Sheriff, M.J., Krebs, C.J. & Boonstra, R. (2009) The sensitive hare: subtle effects of predator stress on reproduction in snowshoe hares. *Journal of Animal Ecology*, **78**, 1249–1258.
- Sheriff, M.J., Krebs, C.J. & Boonstra, R. (2010) The ghosts of predators past: population cycles and the role of maternal effects under fluctuating predation risk. *Ecology*, **91**, 2983–2994.
- Sheriff, M.J., Krebs, C.J. & Boonstra, R. (2011) From process to pattern: how fluctuating predation risk impacts the stress axis of snowshoe hares during the 10-year cycle. *Oecologia*, **166**, 593–605.
- Sheriff, M.J., Wheeler, H., Donker, S.A., Krebs, C.J., Palme, R., Hik, D. & Boonstra, R. (2012) Mountain-top and valley-bottom experiences: the stress axis as an integrator of environmental variability in arctic ground squirrel populations. *Journal of Zoology*, **287**, 65–75.
- Shultz, M.T. & Kitaysky, A.S. (2008) Spatial and temporal dynamics of corticosterone and corticosterone binding globulin are driven by environmental heterogeneity. *General and Comparative Endocrinology*, **155**, 717–728.
- Silverin, B. (1997) The stress response and autumn dispersal behaviour in willow tits. *Animal Behaviour*, **53**, 451–459.
- Silverin, B. (1998) Behavioural and hormonal responses of the pied flycatcher to environmental stressors. *Animal Behavior*, **55**, 1411–1420.
- Solberg, L.C., Baum, A.E., Ahmadiyeh, N., Shimomura, K., Li, R., Turek, F.W., Takahashi, J.S., Churchill, G.A. & Redei, E.E. (2006) Genetic analysis of the stress-responsive adrenocortical axis. *Physiological Genomics*, **27**, 362–369.
- Sterner, R.W. & Ellser, J.J. (2002) *Ecological Stoichiometry*. Princeton University Press, Princeton, NJ.
- Szyf, M., McGowan, P. & Meaney, M.J. (2008) The social environment and the epigenome. *Environmental and Molecular Mutagenesis*, **49**, 46–60.
- Thiel, D., Jenni-Eiermann, S., Braunisch, V., Palme, R. & Jenni, L. (2008) Ski tourism affects habitat use and evokes a physiological stress response in capercaillie *Tetrao urogallus*: a new methodological approach. *Journal of Applied Ecology*, **45**, 845–853.
- Travers, M., Clinchy, M., Zanette, L., Boonstra, R. & Williams, T. (2010) Indirect predator effects on clutch size and the cost of egg production. *Ecology Letters*, **13**, 980–988.
- Uller, T. & Olsson, M. (2006) Direct exposure to corticosterone during embryonic development influences behaviour in an ovoviviparous lizard. *Ethology*, **112**, 390–397.
- Wasser, S.K., Keim, J.L., Taper, M.L. & Lele, S.R. (2011) The influences of wolf predation, habitat loss, and human activity on caribou and moose in the Alberta oil sands. *Frontiers in Ecology and the Environment*, **9**, 546–551.
- Weaver, I.C., Cervoni, N., Champagne, F.A., D'Alessio, A.C., Sharma, S., Seckl, J.R., Dymov, S., Szyf, M. & Meaney, M.J. (2004) Epigenetic programming by maternal behavior. *Nature Neuroscience*, **7**, 847–854.
- Weaver, I.C., Champagne, F.A., Brown, S.E., Dymov, S., Sharma, S., Meaney, M.J. & Szyf, M. (2005) Reversal of maternal programming of stress responses in adult offspring through methyl supplementation: altering epigenetic marking alters life. *Journal of Neuroscience*, **25**, 11045–11054.
- Weaver, I.C., D'Alessio, A.C., Brown, S.E., Hellstrom, I.C., Dymov, S., Sharma, S., Szyf, M. & Meaney, M.J. (2007) The transcription factor nerve growth factor-inducible protein A mediates epigenetic program-

- ming: altering epigenetic marks by immediate-early genes. *The Journal of Neuroscience*, **27**, 1756–1768.
- Welberg, L.A.M. & Seckl, J.R. (2001) Prenatal stress, glucocorticoids and the programming of the brain. *Journal of Neuroendocrinology*, **13**, 113–128.
- Welberg, L.A.M., Seckl, J.R. & Holmes, M.C. (2001) Prenatal glucocorticoid programming of the brain corticosteroid receptors and corticotrophin-releasing hormone: possible implications for behaviour. *Neuroscience*, **104**, 71–79.
- Welcker, J., Harding, A.M.A., Kitaysky, A.S., Speakman, J.R. & Gabrielsen, G.W. (2009) Daily energy expenditure increases in response to low nutritional stress in an Arctic-breeding seabird with no effect on mortality. *Functional Ecology*, **23**, 1081–1090.
- Wikelski, M. & Cooke, S.J. (2006) Conservation physiology. *Trends in Ecology and Evolution*, **21**, 38–46.
- Williams, T.D. (2008) Individual variation in endocrine systems: moving beyond the ‘tyranny of the Golden Mean’. *Philosophical Transactions of the Royal Society B*, **363**, 1687–1698.
- Wingfield, J.C. (1994) Regulation of territorial behavior in the sedentary song sparrow, *Melospiza melodia morphna*. *Hormones and Behavior*, **28**, 1–15.
- Wingfield, J.C. (2005) The concept of allostasis: coping with a capricious environment. *Journal of Mammalogy*, **86**, 248–254.
- Wingfield, J.C. (2008) Comparative endocrinology, environment and global change. *General and Comparative Endocrinology*, **157**, 207–216.
- Wingfield, J.C. & Hunt, K.E. (2002) Arctic spring: hormone-behavior interactions in a severe environment. *Comparative Biochemistry and Physiology B*, **132**, 275–286.
- Wingfield, J.C. & Sapolsky, R.M. (2003) Reproduction and resistance to stress: when and how. *Journal of Neuroendocrinology*, **15**, 711–724.
- Wingfield, J.C., Maney, D.L., Breuner, C.W., Jacobs, J.D., Lynn, S., Ramenofsky, M. & Richardson, R.D. (1998) Ecological bases of hormone-behavior interactions: the ‘emergency life history stage’. *American Zoologist*, **38**, 191–206.
- Young, A.J., Carlson, A.A., Monfort, S.L., Russell, A.F., Bennett, N.C. & Clutton-Brock, T. (2006) Stress and the suppression of subordinate reproduction in cooperatively breeding meerkats. *Proceedings of the National Academy of Sciences of the United States of America*, **103**, 12005–12010.
- Zhang, S., Lei, F., Liu, S., Li, D., Chen, C. & Wang, P. (2011) Variation in baseline corticosterone levels of Tree Sparrow (*Passer montanus*) populations along an urban gradient in Beijing, China. *Journal of Ornithology*, **152**, 801–806.

Received 12 February 2012; accepted 18 June 2012

Handling Editor: Rudy Boonstra