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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

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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 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

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hypthothalamus-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 degredation 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 11β-hydroxysteroid dehydrogenase type 2 (11β-HSD2; Burton & Waddell 1999; Seckl 2004). 11β-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 11β-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 11β-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 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.

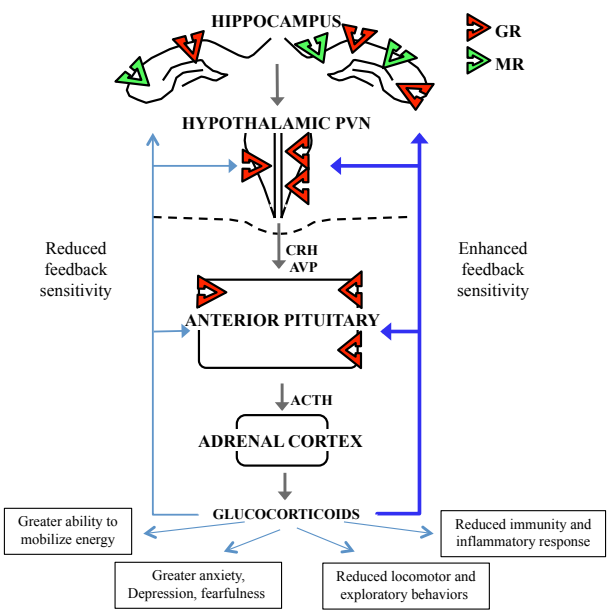

Fig. 1. The hypothalamic-pituitary-adrenal (HPA) axis and negative feedback response of Glucocorticoids (GCs). The sensitivity of the feedback response is due to the level of GCs and the number of GC and mineralcorticoid receptors (GR and MR, respectively) in the brain and GR in the body (de Kloet *et 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.

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

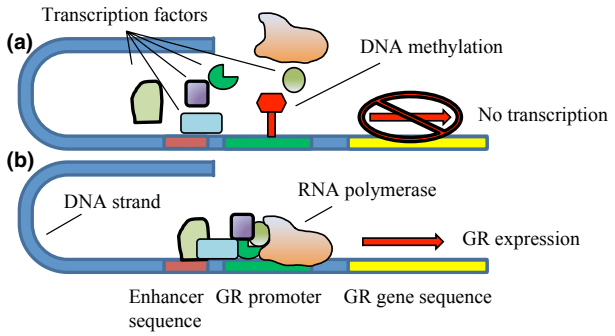

Fig. 2. (a) DNA methylation of glucocorticoid receptor (GR) promoter regions occurs in offspring of low licking and grooming mothers (decreased maternal care associated with high GC levels). High levels of DNA methylation of this promoter prevent transcription factor (NGFI-A) binding and greatly reduce 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.

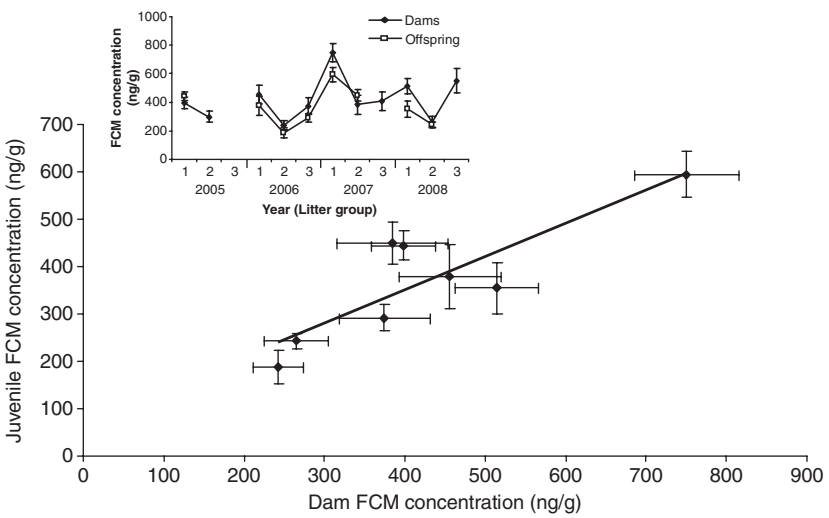

Fig. 3. Faecal cortisol metabolite (FCM) concentration (means ± SE) in free-ranging snowshoe hare dams and juveniles ($r^2 = 0{\cdot}73$, $P = 0{\cdot}007$). Each point is the average from a different litter group (1–3) in 2005–2008. Juveniles were sampled within 1 week of weaning, 28 days after dams (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).

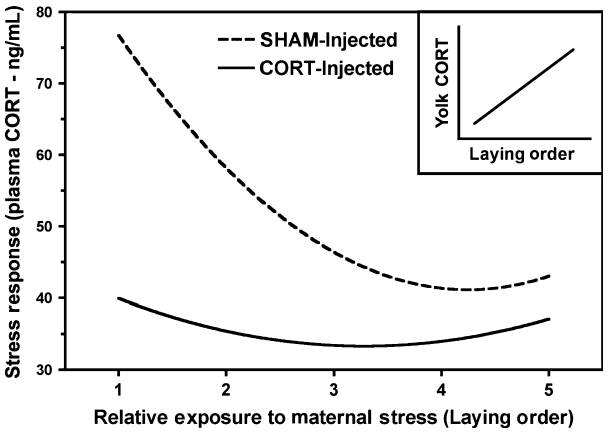

Fig. 4. Relative responsiveness of the stress axis in free-living European starling fledglings in relation to natural variation in exposure to maternal stress (changes in yolk corticosterone across laying order; see Love *et al*. 2008) and an experimental increase in maternal stress (CORT-injections 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; Federenko *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.

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