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Review

Prenatal stress in birds: Pathways, effects, function and perspectives

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ABSTRACT

Although most work on prenatal stress has been conducted on mammalian species, birds provide useful alternative models since avian embryos develop outside the mother's body in a concealed environment, the egg, which is produced during a short time window of 4–14 days. This facilitates measurement of maternal substances provided for and manipulation of the embryo without interfering with the mother's physiology. We critically review prenatal corticosterone mediated effects in birds by reviewing both studies were females had elevated levels of plasma corticosterone during egg formation and studies applying corticosterone injections directly into the egg. A selected review of the mammalian literature is used as background. The results suggest that besides prenatal exposure to corticosterone itself, maternal corticosterone affects offspring's behaviour and physiology via alteration of other egg components. However, results are inconsistent, perhaps due to the interaction with variation in the post-natal environment, sex, age, developmental mode and details of treatment. The potential role of adaptive maternal programming has not been tested adequately and suggestions for future research are discussed.

Contents

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1. Introduction

Stress occurs when an organism experiences allostatic load (McEwen, 2000) which refers to the physiological cost of maintaining physiological stability (homeostasis) in changing environments. Secretion of glucocorticoids increases with allostatic load and in the short run, they are essential for adaptation and maintenance of homeostasis, but if they are elevated over a longer period they exert a cost (allostatic overload) that can lead to adverse health conditions (Wingfield, 2005a; Korte et al., 2005).

Over the past decades there has been an increased scientific interest in the effects of elevated maternal stress levels during pregnancy on the behaviour and physiology of offspring. This has been driven by the discovery of a relationship between maternal stress during pregnancy in humans and the development of physical and mental health disorders in the children of these mothers (for review see Viltart and Vanbesien-Mailliot, 2007). Despite the large amount of research on the effects of maternal stress in offspring of rodents and humans, many questions still remain unresolved, such as vulnerable periods, underlying pathways, duration and consistency of the effects, but also to what extent these maternal effects might be adaptive. The relative inaccessibility of the mammalian foetus to well-controlled experimental manipulations makes it difficult to determine the exact mechanism underlying the effects of prenatal stress. In addition, the use of genetically selected laboratory and highly domesticated animal models might hamper ultimate approaches.

1.1. The advantage of the bird model

Recent research on oviparous species (birds: for references see Tables 1 and 2; fish: McCormick, 1998, 1999; Eriksen et al., 2006; reptiles: Robert et al., 2009; Meylan and Clobert, 2005; Cadby et al., 2010) found consequences of maternal stress on offspring across vertebrate species and it is hypothesised that these maternal effects are due to the transfer of stress hormones (glucocorticoids) from the mother to the egg. Such research is relatively new, but other hormone mediated maternal effects, via androgens, have been widely studied in different bird species and showed that the mother's environment has multiple and long lasting effects on her offspring's phenotype (reviewed in Groothuis et al., 2005; Gil, 2008; Navara and Mendonca, 2008; Von Engelhardt and Groothuis, 2010). The use of birds as alternative models within the field of maternal stress can provide useful information due to the physiology and life history of the bird.

The avian neuroendocrine and endocrine system is very similar to the mammalian system (Wingfield, 2005b) and therefore responds in a similar way to stressors, such as heat, nutrient availability, social interactions and predation. In birds, like in mammals, glucocorticoids are produced by the adrenal glands in response to the pituitary gland's secretion of adrenocorticotropic hormone (ACTH) which production is stimulated by corticotrophin-releasing hormone (CRH). In birds, the embryo with its extra embryonic membranes develops within a shelled egg. Interestingly, these extra embryonic membranes have similar functions as the extra embryonic membranes that form part of the placenta and umbilical cord in mammals, such as regulation of gas and water exchange, remove metabolic waste and steroid metabolism (Antila et al., 1984; Parsons, 1970). The effects of maternal stress and the underlying mechanism might therefore be very similar to those in mammals.

The bird embryo develops outside the mother's body in an egg that has been produced within a short time window (around 4–14 days depending on the species, e.g. Roudybush et al., 1979). This facilitates not only correlation of egg variables, such as nutrients and hormones, with the offspring's phenotype, but also with the mother's condition during egg formation. Additionally, in contrast to mammals, where the foetal environment is difficult to access and manipulate, the egg can be manipulated independently of the mother and therefore provides an easy model for testing different hypotheses on the mechanisms underlying the effects of maternal stress.

Another advantage of avian species is that their level of behaviour is equal in complexity to mammalian species yet they are generally more conspicuous and approachable in natural environments (Konishi et al., 1989). This facilitates research in an adaptive or evolutionary framework, although most work cited in this review has been done on domesticated birds.

There is increasing evidence that environmental stressors can have stimulatory and beneficial effects at low exposure while being detrimental at high levels (Costantini et al., 2010a). These so called hormetic responses might increase an animal's phenotypic plasticity and thereby also its fitness, if early exposure to low levels of stress primes an animal to better cope with stress later in life (conditioning hormesis, Calabrese et al., 2007). In line with this, Gluckman and Hanson (2004) suggested that the prenatal environment provides the developing foetus with an important source for predicting the environment it will be exposed to postnatally. Based on the information the animal receives prenatally, its physiology would adapt in a way that is advantageous in the predicted future environment. When this predictive adaptive response (PAR) is correct, the phenotype would be normal. However, when there is a mismatch between the signals obtained in the prenatal environment during critical developmental periods and the postnatal environment, the adaptive response would become inappropriate, leading to disease. Thus, the pathologies seen in offspring of stressed mammalian mothers might be due to a mismatch between the offspring's prenatal and postnatal environment. In most studies so far, it is often unclear how the effects of maternal stress experienced early in life relate to the postnatal test environments in which the offspring's phenotype is assessed. It is therefore often difficult to conclude whether an observed phenotype reflects adap-

Table 1
Effects of elevated maternal corticosterone on avian offspring's physiology.

Physiological traits	Effect	Species	Age of testing	Reference	Mothers' treatment
Mass					
Hatching mass	=	Chicken		Janczak et al. (2007a)	Unpredictable feeding
	=	Japanese quail		Hayward and Wingfield (2004)	Corticosterone implants
	↓♂ =♀	European starling		Love et al. (2005)	Corticosterone implants
	=	Japanese quail ♂		Satterlee et al. (2007)	Corticosterone implants
	↓	Chicken		Henriksen et al. (submitted for publication)	Corticosterone implants
Post hatching mass	=	Chicken	1–26 weeks	Janczak et al. (2007a)	Unpredictable feeding
	↓/=	Japanese quail	0–6 days/Adulthood[a]	Hayward and Wingfield (2004)	Corticosterone implants
	↓♂=♀/=	European starling	0–5 days/ 10–17 days	Love et al. (2005)	Corticosterone implants
	=	Japanese quail ♂	6 weeks	Satterlee et al. (2007)	Corticosterone implants
	↓/=	Chicken	0–17 days/29 days–12 weeks	Henriksen et al. (submitted for publication)	Corticosterone implants
	↓	Japanese quail	0–30 days[a]	De la Cruz et al. (1987)	Oral administration
Morphology					
Structural size	=	European starling	Hatching	Love et al. (2005)	Corticosterone implants
	=	Chicken	12 weeks	Henriksen et al. (submitted for publication)	Corticosterone implants
Developmental instability	=	Japanese quail ♀	130 days	Satterlee et al. (2008)	Corticosterone implants
Endocrinology					
Baseline corticosterone	=/=	Chicken	11 weeks/7 months♂	Henriksen et al. (submitted for publication)	Corticosterone implants
HPA-axis response	↑	Japanese quail	8 weeks	Hayward and Wingfield (2004)	Corticosterone implants
	=	Chicken	11 weeks	Henriksen et al. (submitted for publication)	Corticosterone implants
Baseline testosterone	↑/=	Chicken	11 weeks/7 months♂	Henriksen et al. (submitted for publication)	Corticosterone implants
Immunocompetence	↓♂=♀	European starling	17 days	Love et al. (2005)	Corticosterone implants
	↓	Chicken	11 weeks	Henriksen et al. (submitted for publication)	Corticosterone implants
Secondary sex ratio	↓	European starling	Hatching	Love et al. (2005)	Corticosterone implants
Reproductive organ size and function	↓[b]	Japanese quail ♂	6–15 weeks	Satterlee et al. (2007)	Corticosterone implants

[a] No statistics.
[b] Reduced cloacal gland volume and functionality.

tive adjustments, phenotypic mismatch or a pathological outcome. Birds are classical models for studies on behavioural ecology and fitness and exhibit a wide range of adaptations to different ecological niches (Konishi et al., 1989). They are therefore excellent model species for testing potentially adaptive effects of maternal stress in different environments.

1.2. Topics of this paper

In this article we review the current literature on the prenatally induced effects of maternal stress in birds and compare these finding to what is known from the mammalian literature, the latter based on a selection of review papers. The term "stress" is widely used and often ill defined. In order to limit the field and look at effects that have been mediated via similar pathways, we will only look at studies where the mother's plasma corticosterone levels were elevated and measured during egg formation or studies where the applied stressor has been shown to elevate plasma corticosterone concentrations in female birds. Several studies have been performed on lines selected for elevated corticosterone response. However, using artificially selected lines has disadvantages such as the fact that it always co-selects for other traits so it becomes difficult to disentangling the effect of maternal stress itself from genetic effects on other maternal components (for a critical discussing of the use of selection lines see Stamps and Groothuis, 2010). Moreover, eggs for the F1 generation were not necessarily produced while the mothers had elevated plasma corticosterone levels. Therefore, we do not include these results. In order to exam-

Table 2
Effects of elevated maternal corticosterone on avian offspring's behaviour.

Behavioural traits	Effect	Species	Age of testing	Reference	Mothers' treatment
Fearfulness					
Tonic immobility					
- *Number of inductions*	=	Chicken	15 days	Davis et al. (2008)	Corticosterone implants
	=	Chicken	30 days - 6 months	Henriksen et al. (submitted for publication)	Corticosterone implants
- *Duration*	↑	Chicken	22 weeks	Janczak et al. (2007a)	Unpredictable feeding
	=	Chicken	15 days	Davis et al. (2008)	Corticosterone implants
	↓	Chicken	30 days - 6 months	Henriksen et al. (submitted for publication)	Corticosterone implants
Anxiety					
Hole-in-the-wall Box	↑	Chicken	15 days	Davis et al. (2008)	Corticosterone implants
Open field	=	Chicken	14 days	Henriksen et al. (submitted for publication)	Corticosterone implants
Competition					
Ability to compete for food	↓	Chicken	23 weeks	Janczak et al. (2007a)	Unpredictable feeding
	↓	Chicken	9 days	Henriksen et al. (submitted for publication)	Corticosterone implants

ine evidence for possible mechanisms we also review the literature on the effects of maternal corticosterone levels on egg composition, and discuss how these compare to the hypotheses that have been put forward in the mammalian literature. Finally, we review studies in which the developing embryo was exposed to elevated levels of prenatal corticosterone by injecting eggs with corticosterone and discuss the biological validity of these studies.

2. Offspring effects of elevation of maternal or foetal glucocorticoids in mammals

2.1. Offspring effects of elevation of maternal glucocorticoids in mammals

In mammals, it has been suggested that stressful events occurring during pregnancy might affect various aspects of the offspring's neuroendocrine system and that this stress-induced modification of the offspring's phenotype ultimately results in the development of long-term diseases (Cottrell and Seckl, 2009). A considerable number of experiments have therefore been performed in animal models, such as primates and rodents (mainly rats) in an attempt to determine whether maternal stress causes permanent alterations in the function of the HPA-axis. The main glucocorticoid is cortisol in humans and primates, and corticosterone in rodents and adult birds and both hormones will be referred to as CORT in the rest of this article. A large number of studies found that rats whose mothers had elevated CORT levels during pregnancy have no differences in basal morning resting levels of plasma CORT but show increased hypothalamic–pituitary–adrenal (HPA) axis activity in response to a stressor (Weinstock, 2005). Prenatal stress in rats has also been shown to correlate with structural and functional changes in the limbic system (a set of brain structures responsible for e.g. emotion, behaviour and long-term memory) and the prefrontal cortex (a brain region involved in planning complex cognitive behaviour and in the expression of personality and appropriate social behaviour) and might explain the altered behaviour seen in these animals, such as learning and memory deficits and increased anxiety (Weinstock, 2008). While low birth weight has often been used as an indicator of prenatal stress in humans, the majority of studies on mice and rats did not find any difference in birth weight (or number of pups) in offspring of stressed mothers (reviewed by Weinstock, 2008) and in those that did, the results between studies were inconsistent (reviewed by D'mello and Liu, 2006).

In mammals, the effects on offspring seem to depend on the intensity, duration and timing of maternal glucocorticoid elevation. Data from studies in mice and rats indicate that alterations in programming of the HPA-axis of the offspring are only seen if the maternal stress is of sufficient intensity and if CORT is elevated at least once daily between days 14 and 21 of gestation (Weinstock, 2008). The impact of prenatal stress can vary across species and sex, as has for example been demonstrated in studies on offspring's immune function (Shanks and Lightman, 2001) and HPA axis activity (Weinstock, 2008). Some traits might be more susceptible to maternal glucocorticoids than others which is illustrated by the fact that gestational stress of shorter duration at a later time during foetal development can still induce fear of novelty and learning deficits in rats even if no difference in the offspring's HPA axis is found (Weinstock, 2008). Finally the method by which a trait is assessed can influence the degree of change that is measured (Shanks and Lightman, 2001; review by Weinstock, 2008).

Therefore, despite a general assumption that gestational stress leads to increased HPA-axis activity, decreased immunity, increased anxiety and memory and learning deficits, the complex effects of maternal stress depending on the intensity of the stressor (probably related to the strength of the maternal CORT response) and sex (probably related to the interaction between CORT and gonadal hormones as CORT can have effects on sexual differentiation: Kaiser and Sachser, 2005) and age of the offspring (determining vulnerability of the CNS and the HPA axis) makes it difficult to make precise prediction for the effect prenatal stress might have in birds.

2.2. Effect of direct foetal glucocorticoid elevation in mammals

Glucocorticoids are involved in prenatal organ maturation (Fowden et al., 1998), and are therefore crucial for the successful transition from the prenatal to the postnatal life. As a consequence, synthetic glucocorticoids have been administered to women in preterm labour in order to improve neonatal viability (Liggins and Howie, 1972). However studies in both humans and animals have demonstrated that this type of treatment can have long term effect on other aspects of the offspring. Treating mothers with synthetic glucocorticoids during gestation has been shown to reduce the offspring's birth weight (reviewed by Sloboda et al., 2005) cause permanent hypertension (reviewed by Nuyt, 2008), hyperglycaemia and hyperinsulinemia (reviewed by O'Regan et al., 2001), increased HPA-axis activity (Kapoor et al., 2008; Tegethoff et al., 2009), and anxiety-like behaviour in adult offspring (Kanitz et al., 2003; Chung et al., 2005; Drake et al., 2005, 2007; Sloboda et al., 2005; Jarvis et al., 2006), with the effects being most prominent when the synthetic glucocorticoid treatment is applied in the last third of gestation (Welberg et al., 2001). Unlike corticosterone and cortisol, synthetic glucocorticoids, like dexamethasone and betamethasone, can readily cross the placental barrier and reach the foetus without being inactivated by the enzyme 11β-Hydroxysteroid Dehydrogenase (11β-HSD; Seckl, 1997). These types of studies might therefore resemble CORT egg-injection studies (Section 4) more closely than maternal stress studies. Although synthetic glucocorticoids have a different affinity to the relevant receptors, (Wilckens, 1995; Sapolsky et al., 2000), the above mentioned literature indicates that synthetic glucocorticoids are effective and mirror corticosterone or cortisol effects.

3. Offspring effects of elevation of maternal glucocorticoids in birds

Different methods have been applied to elevate plasma CORT levels in avian females in order to look at the effects on offspring. Similar to mammalian research, we include in this review bird studies where the mother has been exposed to a stressor that elevated plasma CORT levels (unpredicted feeding regime, Janczak et al., 2007a) and studies were the mothers plasma CORT levels have been directly elevated either by subcutaneous CORT-implantation (Hayward and Wingfield, 2004; Love et al., 2005; Satterlee et al., 2007, Henriksen et al., submitted for publication) or oral administration (de la Cruz et al., 1987). Most of these studies have been performed on precocial species such as chickens (*Gallus gallus domesticus*) and Japanese quails (*Coturnix japonica*), contrary to mammalian studies where most research has been done on altricial species. Potential effects of elevated plasma CORT concentrations in female birds on the next generation have been investigated both by measuring the offspring's physiological traits (Table 1) and behavioural traits (Table 2).

3.1. Effects on avian offspring's physiology

Studies measuring physiological traits in avian offspring of stressed mothers have mainly looked at different aspects of growth, such as hatching mass (Janczak et al., 2007a; Hayward and Wingfield, 2004; Love et al., 2005; Satterlee et al., 2007; Henriksen et al., submitted for publication), structural size (Love et al., 2005; Henriksen et al., submitted for publication), growth both before

Table 3
Effects of elevated female corticosterone on egg composition.

Egg variable	Effect	Species	Reference	Mothers' treatment
Mass				
Egg mass	↓	Chicken	Rozenboim et al. (2007)	Heat stress
	=/↓	Chicken	Downing and Bryden (2008)	Handling/Heat stress
	=	Zebra finch	Salvante and Williams (2003)	Corticosterone implants
	=	Japanese quail	Hayward and Wingfield (2004)	Corticosterone implants
	=	European starling	Love et al. (2005)	Corticosterone implants
	↓	Chicken	Henriksen et al. (submitted for publication)	Corticosterone implants
Yolk mass	↓ (follicle)	Chicken	Rozenboim et al. (2007)	Heat stress
	=	Zebra finch	Salvante and Williams (2003)	Corticosterone implants
	↓	Chicken	Henriksen et al. (submitted for publication)	Corticosterone implants
Albumin mass	=/↓	Chicken	Downing and Bryden (2008)	Handling/Heat stress
	=	Zebra finch	Salvante and Williams (2003)	Corticosterone implants
	↓ (albumin+shell)	Chicken	Henriksen et al. (submitted for publication)	Corticosterone implants
Shell mass	=	Zebra finch	Salvante and Williams (2003)	Corticosterone implants
Lipid, protein concentration				
Yolk lipids	=	Zebra finch	Salvante and Williams (2003)	Corticosterone implants
Yolk protein/Albumin protein	=/=	Zebra finch	Salvante and Williams (2003)	Corticosterone implants
Hormone concentration				
Yolk corticosterone	=	Chicken	Janczak et al. (2007a)	Unpredictable feeding
	=	Chicken	Cook et al. (2009)	ACTH-injection
	↑	Japanese quail	Hayward and Wingfield (2004)	Corticosterone implants
	↑	European starling	Love et al. (2005)	Corticosterone implants
Albumin corticosterone	↑/↑/↑	Chicken	Downing and Bryden (2008)	Handling/Heat stress/Injection
	=	Chicken	Cook et al. (2009)	ACTH-injection
Yolk A/G/E[a]	↓/↓/=	Chicken	Henriksen et al. (submitted for publication)	Corticosterone implants

[a] A: yolk androgens, G: yolk gestagens, E: yolk estrogens.

(Janczak et al., 2007a; Hayward and Wingfield, 2004; Love et al., 2005; Henriksen et al., submitted for publication) and after sexual maturity (Hayward and Wingfield, 2004; Satterlee et al., 2007), and developmental stability (Satterlee et al., 2008). The latter was assessed by measuring fluctuating asymmetry (FA), believed to be stress-induced deviations from morphological bilateral symmetrical traits (Parsons, 1990; Møller and Swaddle, 1997; Thomson, 1999).

The effect of maternal CORT elevation on their offspring's endocrine state has also been investigated by measuring the offspring's baseline plasma testosterone and CORT levels (Henriksen et al., submitted for publication), as well as their HPA-axis response (Hayward and Wingfield, 2004; Henriksen et al., submitted for publication) when exposed to a stressful situation. Immunocompetence was also evaluated in these offspring, either via a T-cell mediated inflammatory response to phytohemagglutinin (PHA, Love et al., 2005) or B-cell mediated production of antibodies during an antigen challenge (sheep red blood cell challenge, Henriksen et al., submitted for publication). The fitness of male offspring has been evaluated by measuring their reproductive function (size and functionality of reproductive organs, Satterlee et al., 2007), while secondary sex ratio has been investigated to see if survival chances differ between the sexes when prenatally exposed to maternal stress (Love et al., 2005). Most of these traits have only been assessed in one or two studies making it impossible to give an indication of how general and consistent the findings are.

In all the studies that found an effect of elevated maternal CORT on offspring's body mass, the results were always a lower body mass (Table 1). Two out of five studies reported a lower hatching mass in offspring of stressed mothers (Love et al., 2005; Henriksen et al., submitted for publication), four out of six studies reported lower body mass later in life (Hayward and Wingfield, 2004; Love et al., 2005; Henriksen et al., submitted for publication; de la Cruz et al., 1987) and none reported an increase in body mass. The two studies that did not find any difference in body mass post hatching between offspring of control and stressed mothers (Janczak et al., 2007a; Satterlee et al., 2007) also did not find any difference in body mass at hatching. Elevated maternal CORT during egg formation therefore seems to have the potential to reduce the prenatal, and especially the postnatal growth of the offspring that hatch from these eggs. The weaker effect on embryonic growth is also indicated by the fact that elevated plasma CORT in mothers only lowered egg mass in three (Rozenboim et al., 2007; Downing and Bryden, 2008) of six studies (Table 3, Section 4.1) and egg mass is highly correlated with hatching mass in birds (Nisbet, 1978; Stokland and Amundsen, 1988; Amundsen and Stokland, 1990). Love et al. (2005) reported lower body mass in male offspring of stressed mothers, but no difference in the structural size of the offspring which indicates a lower energetic body condition.

In three studies (Hayward and Wingfield, 2004; Love et al., 2005; Henriksen et al., submitted for publication) the lower body mass in offspring of mothers with elevated plasma CORT disappeared before the birds reached sexual maturity. This can be obtained by a slower steady growth over a longer time period, or by a period of catch-up growth. The distinction between the two is important because of potential costs associated with catch-up growth. While early in life catch-up growth might be beneficial for the offspring since being smaller than conspecifics could have potential fitness costs, such as reaching sexual maturity later and being less able to compete for resources (see Table 2), catch-up growth has been reported to induce a wide range of cost to the individual, many of which are likely to be interlinked (for review see Metcalfe and Monaghan, 2001). In zebra finches (*Taeniopygia guttata*), catch-up growth has been shown to impair adult cognitive performance (Fisher et al., 2006) and in humans, fast catch-up growth early in life has been shown to correlate with increased risk of health-problems, possibly due to a change in allocation of resources (Ozanne and Nicholas, 2005). Catch-up growth could therefore explain the lower immunocompetence in offspring of stressed mothers reported in the studies by Love et al. (2005) and Henriksen et al. (submitted for publication). However, whether the deleterious effects are a direct result of this catch-up growth or of the impairment of growth itself during or before the phase of catch-up growth is yet unclear.

Growth rates are flexible and are usually regulated at an optimal rather than maximal rate (Arendt, 1997). One could hypothesise

that the post-hatch environment might influence the speed of catch-up growth or the length of the growth period after hatching. Being small early in life might be an adaptive response that increases survival chances in a hostile environment where food is scarce or difficult to obtain. However, if the postnatal environment is non-stressful and therefore does not match the prediction given in the prenatal environment, a longer growth period or a fast catch-up, despite the potential cost, might be more favourable. This would mean that the effects of prenatally induced maternal stress are determined by the interaction of the pre- and post hatching environment, a topic hardly explored in birds (but see Section 4).

It has been assumed that a perfectly symmetrical organism is the ideal for which a developmental program is striving (Polak and Trivers, 1994) and that developmental stability is the ability of an animal to buffer its development against random disruptors, such as stress (Waddington, 1942; Lerner, 1954). Prenatal CORT exposure has been proposed to increase developmental instability in birds (Eriksen et al., 2003 see Section 4.2.2). The only study so far that investigated developmental stability in offspring of mothers with elevated CORT by looking at fluctuating asymmetry between the right and left tarsus length and right and left distance between the auditory canal and the nares found no effect in females offspring (Satterlee et al., 2008). Males where not tested in this study.

Surprisingly, only two studies (Hayward and Wingfield, 2004; Henriksen et al., submitted for publication) have looked at alterations in the offspring's HPA-axis response, a trait commonly tested in mammals. The elevated HPA-axis response to a stress test in the study by Hayward and Wingfield (2004) indicates that stress in female birds can potentially influence their offspring's endocrinology. Other parts of the offspring's endocrinology might also be affected as demonstrated by the elevated baseline plasma testosterone levels found in chickens of mothers with elevated CORT (Henriksen et al., submitted for publication). Such effects can potentially interact with a wide array of other physiological traits, such as immune function, as well as behavioural traits, such as fearfulness (see next section).

The reduced size and functionality of the reproductive organs (cloacal gland volume and foam production) reported in male quails of mothers with elevated CORT levels (Satterlee et al., 2007), and the lower antibody response in such offspring (see above) might indicate that maternal stress negatively affects the fitness of their male offspring.

Consistent with the latter, experimentally elevated maternal CORT levels in female European starlings (*Sturnus vulgaris*) resulted in a female biased brood at hatching, caused by elevated embryonic mortality in males (Love et al., 2005). This indicates a sex-specific difference in sensitivity to the mothers' plasma CORT levels (see Section 3.4.2). In addition to this effect on the secondary sex ratio, induced after fertilization, avian mothers can also bias the primary sex ratio of their offspring at fertilization by producing unequal numbers of male and female embryos. This is possible because the avian female is the heterogamic (ZW) sex and potentially in control of non-random sex chromosome segregation during meiosis (meiotic drive; for a review of avian offspring sex ratio manipulation see Alonso-Alvarez, 2006). Although the underlying physiological mechanisms remains obscure, several studies suggest that this primary sex ratio is under the control of maternal plasma CORT levels (Pike and Petrie, 2006; Bonier et al., 2007; Muller et al., submiitted for publication).

In conclusion, there seems to be a general trend for reduced body mass in offspring of mothers with elevated CORT and similar to mammalian studies, maternal plasma CORT levels in birds have the potential to modulate the offspring's immunocompetence and endocrinology. In addition there is evidence that maternal CORT biases the sex ratio of the offspring to daughters and reduces reproductive function in males. These alterations are likely to influence the offspring's fitness (see Section 5.3 for further discussion).

3.2. Effects on avian offspring's behaviour

Studies looking at possible effects of prenatal maternal stress on offspring's behaviour have only been conducted in chickens (*Gallus gallus domesticus*), testing the offspring's level of anxiety, fearfulness and ability to compete for food (Table 2). Anxiety has been assessed via isolation tests such as open field test and hole-in-the-wall test while fearfulness has been assessed via tonic immobility tests. Isolation tests act as anxiogenic stimuli and allow for measurement of anxiety-induced decrease in locomotion activity and exploratory behaviours. Tonic immobility is a catatonic-like state of reduced responsiveness induced by physical restraint, and the duration of tonic immobility is considered a measure of fearfulness in birds (Jones, 1986, 1989). It is thought to be a defence strategy evolved to reduce the predators' interest in the prey, when the prey stops moving after it has been caught. The interpretation of these tests in terms of motivation is, however, open for discussion. The results of these studies are inconsistent since maternal stress has been reported to increase and decrease fear behaviour, increase anxiety in offspring or have no effect at all. It is therefore not possible to make a general statement on the effect of maternal stress on fearfulness and anxiety in birds.

The two studies that measured offspring's ability to compete for food both reported reduced competitive ability in offspring of stressed mothers (Table 2). Both studies applied a similar test design by letting a control bird and an offspring of a stressed mother compete for food against each other. Offspring were tested at 9 days of age in the study by Henriksen et al. (submitted for publication) and at sexual maturity in the study by Janczak et al. (2007a), the latter suggesting long-term effects. The underlying behaviour or physiology that causes this difference however is unclear. As no difference in body mass was found in the study with adult birds, smaller body size can not be responsible for the findings. Perhaps elevation of anxiety or fear, or a difference in hunger motivation is responsible for these results. The reduced competitiveness in the offspring of stressed mothers could potentially lower the offspring's fitness, since in a natural environment where food might be limited, a reduced ability to compete for food in a social species like fowl would come at a cost. It could, however, also be that offspring of stressed mothers have lower metabolic rate and therefore need less food, which would make them more adapted to an environment were food is scarce.

Behavioural studies on offspring of avian mothers with elevated plasma CORT are clearly very much missing from the current literature. It is therefore difficult to make generalizations, let alone to conclude whether the changes in offspring traits are adapted to a stressful situation. The latter difficulty is enlarged by the possibility that this depends both on the surrounding environment (matching versus mismatching, see below) and which physiological and behavioural changes are linked to each other, making up the coping style or personality of the animal (Stamps and Groothuis, 2010). It has now been demonstrated in a wide array of taxa that individuals of the same species and sex substantially and consistently differ in a wide array of behavioural and physiological traits such as aggression, exploration, anxiety, steroid production and immune system. These linked traits may represent different strategies to cope with environmental stressors, being maintained by frequency or habitat dependent selection. As a consequence, one cannot generalize that a particular trait expression, or even one type of animal, is always

better adapted than another. For an excellent review on this topic see Korte et al. (2005).

3.3. Possible explanation for inconsistency in results between studies

There are several possible explanations for the inconsistencies in the results discussed above. First, although all of the studies reported in Tables 1 and 2 elevated mother's plasma CORT within the physiological range, the offspring still might have hatched from eggs that were produced under different intensities of maternal CORT elevations. Depending on the studies' experimental designs, the female's plasma CORT levels were elevated from four up to nine days, In chickens (*Gallus gallus domesticus*), the major part of egg formation takes about 8–9 days (Romanoff and Romanoff, 1949; Kritchevsky and Kirk, 1951; Grau, 1976; Gilbert et al., 1983), and since the timing of egg collection differed between studies this might have caused differences in the exposure to maternal CORT the eggs experienced during their formation. Eggs collected shortly after the mother's plasma CORT was elevated would only have been affected during the final stages of egg formation, while eggs collected a week after the beginning of the treatment would have been affected during most of the egg formation period. Given the relatively short duration of maternal CORT elevation, eggs collected two or more weeks after the initiation of the mother's treatment might only have been affected by maternal stress during the early part of egg formation or they might not have been affected at all. While some studies only collected eggs laid 7 days after the beginning of treatment (de la Cruz et al., 1987; Hayward and Wingfield, 2004) others pooled eggs collected over a longer period (Janczak et al., 2007a—day 5–10; Satterlee et al., 2007—day 7–14; Henriksen et al., submitted for publication—day 12–18; Davis et al., 2008—2–3 weeks). The decision on when to collect eggs might be based on the duration of plasma CORT elevation in each single study, but some studies did not measure plasma CORT in the mothers (Rozenboim et al., 2007; Satterlee et al., 2007; Davis et al., 2008), making it difficult to estimate the duration and intensity of maternal CORT elevation during egg formation. The potential differences in duration and intensity of prenatal exposure to maternal stress due to differences in the experimental design between studies might therefore explain some of the inconsistencies seen between studies regarding the offspring's phenotype.

Second, offspring were tested at different life-stages. Quails tested at sexual maturity showed an elevated HPA-axis reactivity when coming from stressed mothers while chickens tested before sexual maturity showed no difference. In chickens, response to an ACTH challenge has been shown to attenuate with age in males (Schmeling and Nockels, 1978). Effects of maternal stress on the offspring may differ in different life stages, and more knowledge about causal mechanisms and functional consequences is needed for predictions regarding age dependent effects. For example impaired growth may induce compensatory growth later of which the costs have to be paid in adulthood. Also, according to the PAR hypothesis, the maternal cue programming the offspring, might only induce phenotypic changes later in life, depending on when this change is likely to be advantageous in the future (Gluckman et al., 2005).

Third, stressed mothers may have some control over their offspring's prenatal environment and thereby can either prevent CORT transfer to the egg (see Section 3.4.2.2) or prevent the effects that an elevation of prenatal CORT exposure would induce depending on her surrounding environment. And finally, the effect of maternal CORT on the offspring may depend on the offspring's postnatal rearing condition, a topic to which we will return in the discussion in Section 5 (but see also Section 4).

3.4. Mechanisms underlying effects of maternal CORT

3.4.1. Possible mechanisms in mammals

In mammals, two major hypotheses have been proposed to underlie the association between maternal stress and postnatal effects in offspring: (1) foetal malnutrition and (2) overexposure to glucocorticoids (Cottrell and Seckl, 2009). These two are not mutually exclusive, as circulating maternal glucocorticoids have been reported to strongly impact the amount of nutrients that are delivered to the foetus and malnutrition affects prenatal glucocorticoid exposure (Cottrell and Seckl, 2009). Therefore, and because foetal exposure to nutrients and CORT are difficult to manipulate independently in mammalian species, the exact mechanism is still an unresolved issue. Few studies have systematically explored mammalian foetal exposure to CORT after maternal stress (Ward and Weisz, 1984; Erisman et al., 1990; Ohkawa et al., 1991). Ward and Weisz (1984) showed a small increase in foetal CORT plasma levels despite a huge increase in maternal CORT, and although maternal and foetal plasma CORT levels both gradually increase in parallel during pregnancy, foetal plasma levels remains 13-fold lower (Gitau et al., 2001). This is probably to a large extent due to the protective efficacy of the placental enzyme 11β-HSD, which catalyzes the conversion of 80% of the active CORT to its inactive 11-oxo forms (cortisone from cortisol, 11-dehydrocorticosterone from corticosterone; Murphy et al., 1974), thereby protecting the embryo against overexposure of maternal CORT.

In mammalian studies, the effects of elevated maternal glucocorticoids have often been reported to be dependent on the sex of the offspring and it has therefore been proposed that the effects of maternal stress might in some cases and to some degree be mediated via sex hormones (Weinstock, 2001), although the mechanisms behind this is not yet clear (Cottrell and Seckl, 2009).

3.4.2. Possible mechanisms in birds

Birds provide better opportunities for disentangling the effects of exposure to less nutrients and elevated CORT on offspring phenotype (see Section 1). This has mainly been done by looking at egg mass in order to determine the amount of available nutrients for the developing embryo and by measuring and manipulating the concentration of CORT in the eggs, as it has been assumed that the effects on the offspring might be due to maternal CORT being transferred from the mothers plasma to the egg, thereby exposing the developing embryo to higher CORT concentration. The composition of eggs laid by females with elevated plasma CORT has been studied both in females that were exposed to a stressor (high ambient temperatures, unpredictable feeding regime) that elevated their plasma CORT and in females with artificially elevated plasma CORT levels (CORT implants or ACTH injection). Injections of CORT *in ovo* will be discussed separately in Section 4.

3.4.2.1. Prenatal nutrition. Although not all studies reported an effect of the female's CORT levels during egg formation on egg mass, all the studies that did showed a decrease in egg, yolk and/or albumin mass (Table 3). Egg formation is a demanding process both in terms of energy and nutrient requirements (Nager, 2006) and it might therefore be adaptive for females in stressful environments to reduce their egg investment, either by laying fewer or smaller eggs. Plasma CORT elevation has been shown to alter the production of yolk precursors in the liver (Salvante and Williams, 2003) inducing reduction of the nutrition value of the egg. Chick mass has been shown to correlate with egg mass (Nisbet, 1978; Stokland and Amundsen, 1988; Amundsen and Stokland, 1990; Finkler et al., 1998) implying that also in birds, maternal stress might to some extent be mediated through malnutrition.

Not only its mass but also the composition of an egg might have considerable impact on the successful development of the embryo

and may influence its subsequent survival. Yolk contains a high percentage of fat which is the primary source of energy for the developing young, while the albumin mainly contains water and simple proteins (Romanoff and Romanoff, 1949). The relative proportions of yolk and albumin in eggs varies greatly among bird species (Carey et al., 1980; Sotherland and Rahn, 1987). In general, the greater the percentage of yolk in the egg the more precocial the chick (Hill, 1993), indicating that investment in egg yolk is necessary for producing more developed offspring (Arnold et al., 1991; Hill, 1993). Metcalfe and Monaghan (2001) have argued that precocial birds, which hatch from the egg fully developed, might be more affected by prenatal nutrition deficits than altricial species, since the individuals cannot compensate during this important developmental period for any nutritional shortcomings. The percentage of yolk and albumin in an egg can also vary within species, depending upon the size of the egg (see ref. in Hill, 1993), so the reported differences in egg size in Table 3 may also reflect differences in yolk/albumin ratio that can potentially influence the development of the embryo. The actual composition of the yolk and albumin might also be important, but so far there has been no indication that lipid or protein composition is changed in yolk or albumin of eggs laid by females with elevated CORT levels (Salvante and Williams, 2003).

There might be another, more indirect way in which egg mass could affect offspring phenotype. Differences in incubation temperature (in industrial incubators) have been shown to relate to egg size (Lourens et al., 2007) and differences in incubation temperature has been shown to affect offspring postnatal HPA-axis response (Durant et al., 2010; Cyr et al., 2007) and growth (Durant et al., 2010; Lay and Wilson, 2002). Therefore, if maternal stress decreases egg size, this might not only affect its composition and the amount of nutrients delivered but also change incubation temperature which in turn can affect embryonic development.

3.4.2.2. Prenatal hormone exposure and related methological issues. It has been hypothesized that in birds, the effects of prenatal exposure to maternal stress is mediated via excess amounts of CORT being transferred from the mother's plasma into the egg during yolk formation or albumin deposition. However, only two out of five studies (Table 3) found an increased concentration of CORT in the yolk of eggs laid by females with elevated plasma CORT during egg formation, and only one (using different stressors) out of three studies found an increase in albumin CORT concentration in eggs laid by females with elevated plasma CORT during egg formation (Table 3). These data suggest that either exposure to maternal CORT varied substantially among studies (see Section 3.3) and/or that under some conditions the mother prevents CORT from being transferred from her plasma to the egg yolk or albumin. A recent study on chicken eggs revealed that gestagens (progesterone, pregnenolone and others), which are present in the yolk in high concentrations, can give a signal in a CORT immunoassay (Rettenbacher et al., 2009). This analytical problem can lead to an overestimation of CORT concentrations in the egg. The amount of authentic CORT in the yolk is generally low, in chickens probably around 0.3 ng/g yolk (assessed via liquid chromatography–mass spectrometry; Sas et al., 2006) and due to the low transfer rate from blood to egg (Rettenbacher et al., 2005) the amount of CORT in the yolk might not always reflect elevations in maternal plasma CORT concentrations.

The enzyme 11β-HSD2, the main glucocorticoid inactivation enzyme in the mammalian placenta, has also been found in the ovary of zebra finches (Katz et al., 2010) and in the gonads and oviduct of chickens (Klusonova et al., 2008). This might explain the possible low transfer rate of CORT from the females' plasma to her eggs and suggests that birds and mammals have similar strategies to protect the embryo from overexposure to maternal CORT. Similarities between the mammalian placenta and the eggs of oviparous species have been proposed earlier. Sulfotransferase activity is known to be very high in the foetal portion of the mammalian placenta (Miki et al., 2002) and to be important in buffering the foetus from maternal steroid signals (Levitz, 1966). A study on the oviparous red-eared slider turtles showed that during early incubation, extra-embryonic membranes produce similar buffering enzymes that also convert steroid hormones into inactive water-soluble forms (Paitz and Bowden, 2008) and similar observations have also been made for birds (Antila et al., 1984; Parsons, 1970; von Engelhardt et al., 2009).

If CORT is prevented (to some extent) from entering the egg, other steroid hormones might be involved in mediating the effect of maternal CORT. Both androgen and gestagen concentrations in the yolk have been shown to decrease in females with elevated plasma CORT (Henriksen et al., submitted for publication). Effects of prenatal gestagen exposure on the avian offspring have not yet been studied, but prenatal androgen exposure has been shown to have multiple and long lasting effects on birds behaviour and physiology (for review see Groothuis et al., 2005; Von Engelhardt and Groothuis, 2010). Female birds deposit different amounts of androgens into their eggs depending on environmental conditions (for a review see Groothuis et al., 2005; Gil, 2008; Von Engelhardt and Groothuis, 2010). The mechanism behind this is not known (Groothuis and Schwabl, 2008). Recent data showed that stress has the potential to decrease the synthesis of gonadal steroids in chickens (Rozenboim et al., 2007) and that elevated plasma CORT affects gonadal hormone concentrations in the yolk (Henriksen et al., submitted for publication). Environmental cues are known to affect plasma CORT levels and these in turn may suppress follicle production of androgens and gestagens and thereby also the amount of these hormones in the egg, providing a mechanism for how environmental factors are translated into yolk concentrations of gonadal hormones. In addition, there are other pathways in which maternal plasma corticosterone might be able to affect the chick. The biological activity of glucocorticoids (CORT) is to a large part dependent on the presence of glucocorticoid receptors (GR). Interestingly, there is evidence that gonadal steroids, such as androgens, estrogens and gestagens are able to modulate the expression and activation of GR (for review on this see Turner, 1997) e.g. large concentrations of progesterone can block GR in chicken embryos (Chader and Reif-Lehrer, 1972). Henriksen et al. (submitted for publication) found that female chickens (*gallus gallus domesticus*) with elevated plasma CORT levels deposit less androgens and gestagens in their eggs. Therefore, even if no difference exist in the concentration of CORT in the eggs of stressed and un-stressed females, the embryos exposure to CORT might still differ due to differences in gonadal steroid concentration in the yolk. This may also explain why effects of maternal plasma CORT are seen in offspring even when CORT itself is not being transferred to the egg.

The explanation above suggests that phenotypic changes reported in offspring of mothers with elevated CORT (Tables 1 and 2) should be similar to what is known about the effects of low prenatal androgen exposure. Indeed, lower yolk androgens correlate with lower growth and competitiveness, (Groothuis et al., 2005), as found in offspring exposed to maternal stress. It therefore seems likely that prenatal androgens could be involved in mediating the effects of maternal CORT elevation. However, since higher levels of prenatal testosterone (e.g. via injections in ovo) decreased immunocompetence (Andersson et al., 2004; Groothuis et al., 2005; Muller et al., 2005) whereas maternal stress, that is supposed to lower yolk androgen levels, also suppressed immunocompetence, maternal stress may be translated to the offspring via multiple pathways. As mentioned before, lower egg mass, body mass or catch-up growth might be detrimental for the immune system, because it is energetically costly to re-allocate energy away from the immune system

towards growth. In addition, it is known that prolonged exposure to elevated CORT, for example triggered by altered HPA-axis responsiveness, may directly modulate the immune system in birds (Raberg et al., 1998).

It should also be noted that some of the egg data comes from studies where offspring phenotype was not tested, and that in some of the offspring studies eggs were not analysed, which make a direct comparison difficult and illustrate the importance of analysing egg variables in the same studies where offspring's phenotype is accessed.

4. Offspring effects of elevation of corticosterone in the egg

Despite the uncertainty about how much plasma CORT is transferred directly from the bird mother's plasma to her eggs, several studies have injected CORT into bird eggs in order to look at the direct effects of prenatal CORT exposure not potentially confounded by other aspects of egg quality. This has been done both in freshly laid eggs by injecting CORT into the albumin or yolk (see Tables 4 and 5) or by injecting CORT into the egg during incubation next to the developing embryo (see Tables 6 and 7). Mammalian studies have found that effects of prenatal CORT exposure differ depending on whether the exposure occurs early or late during gestation, possibly due to differences in tissue maturation. The ability of cells and tissues to respond to CORT is tissue specific and is altered during development (Kalimi, 1984). The presence of GR has been demonstrated as early as day 6 in chicken embryos, and although no increase in cytoplasmic receptor concentration was found during the rest of the incubation period, glucocorticoid-provoked enzymatic activity increases after day 6 (Lippman et al., 1974) indicating that although the concentration of GR does not change during incubation the physiochemical properties of the GR change and increase the effect of CORT. We will therefore discuss studies that injected eggs with CORT before the onset of incubation and during incubation in two separate sections.

4.1. Effect of egg CORT elevation pre-incubation on physiology

CORT has been injected into freshly laid eggs of domesticated chickens (*Gallus gallus domesticus*), Japanese quails (*Coturnix japonica*), Barn swallow (*Hirundo rustica*), European starlings (*Sturnus vulgaris*) and Yellow legged gulls (*Larus michahellis*) (Tables 4 and 5). These types of studies therefore show a much larger variety in study species than studies looking at effects of maternal CORT elevation. Furthermore, one of these studies included alterations in the postnatal environment in order to see if reducing the quality of the postnatal environment (reduced food provision rate by mothers, Love and Williams, 2008a, 2008b) would modulate the effects of prenatal CORT exposure.

The same physiological traits that were investigated in offspring of female birds with elevated plasma CORT levels were also investigated in birds hatching from CORT treated eggs. Again body mass has received most attention, but also growth related traits (plumage development, flight muscle weight, tarsus length and developmental stability), HPA-axis activity, immunity and secondary sex ratio have been assessed (Table 4).

Similar to studies on maternal stress in birds, injecting eggs with CORT seems to impair the bird's growth especially during their post hatching development (Saino et al., 2005; Janczak et al., 2006; Eriksen et al., 2003) and can potentially do this in a sex dependent manner (Hayward et al., 2006), although three out of seven studies did not report a treatment effect (Rubolini et al., 2005; Janczak et al., 2007b; Chin et al., 2009). Only one (Love and Williams, 2008a) out of four studies (Eriksen et al., 2003; Rubolini et al., 2005; Janczak et al., 2006; Love and Williams, 2008a) found a sex-specific lowering of hatching mass.

Consistent with the suppression of growth, structural size (tarsus length) was reduced and plumage development was delayed in barn swallow chicks from CORT injected eggs (Saino et al., 2005). However, flight muscle weight was increased in another altricial species, the European starling (Chin et al., 2009). In the chicken,

Table 4
Effect of egg corticosterone elevation pre-incubation on physiology.

Physiological traits	Effect	Species	Age of testing	Reference	Injection (site and amount)	
Mass						
Hatching mass	=	Yellow legged gull		Rubolini et al. (2005)	Albumin	15 ng/egg
	=	Chicken		Janczak et al. (2006)	Albumin	10 ng/ml
	↓♂,=♀	European starling		Love and Williams (2008a)	Yolk	12.8 ng/g
	=	Chicken		Eriksen et al. (2003)	Egg	0.6–1.2 μg/ml
Post hatching mass	=	Yellow legged gull	1–20 days	Rubolini et al. (2005)	Albumin	15 ng/egg
	↓	Barn swallow	4–7 days	Saino et al. (2005)	Albumin	0.5 ng/egg
	↓	Chicken	1–4 weeks	Janczak et al. (2006)	Albumin	0.6 μg/egg
	=	Chicken	3 weeks	Janczak et al. (2007b)	Albumin	5.5 ng/ml
	↓♂,=♀	Japanese quail	0–8 days	Hayward et al. (2006)	Yolk	1.79 ng/g
	=	European starling	Fledging	Love and Williams (2008a)	Yolk	12.8 ng/g
	↓	Chicken	3–11 weeks	Eriksen et al. (2003)	Egg	10–20 ng/ml
Morphology						
Plumage development	↓	Barn swallow	12 days	Saino et al. (2005)	Albumin	0.5 ng/egg
Structural size	↓	Barn swallow	12 days	Saino et al. (2005)	Albumin	0.5 ng/egg
Flight muscle weight	↑	European starling	21 days	Chin et al. (2009)	Yolk	15.4–28.3 ng/g
Developmental instability	↑	Chicken	11 weeks	Eriksen et al. (2003)	Egg	10–20 ng/ml
Endocrinology						
Baseline corticosterone	=	Japanese quail	8 weeks	Hayward et al. (2006)	Yolk	1.79 ng/g
	=	European starling	15 days	Love and Williams (2008a)	Yolk	12.8 ng/g
HPA-axis response	=♂, ↓♀	Japanese quail	8 weeks	Hayward et al. (2006)	Yolk	1.79 ng/g
	↓	European starling	15 days	Love and Williams (2008a)	Yolk	12.8 ng/g
Immunity	=(vaccine)	Yellow legged gull	4–15 days	Rubolini et al. (2005)	Albumin	15 ng/g
	↓ (PHA),	Yellow legged gull	8 days	Rubolini et al. (2005)	Albumin	15 ng/g
	♂ ↑NC, ↓C[a]	European starling	15 days	Love and Williams (2008b)	Yolk	12.8 ng/egg
	♀ ↓NC,=C[a]	European starling	15 days	Love and Williams (2008b)	Yolk	12.8 ng/egg
Secondary sex ratio	=	European starling	Hatching	Love and Williams (2008a)	Yolk	12.8 ng/egg
	=NC, ↓C[a]	European starling	Fledging	Love and Williams (2008a)	Yolk	12.8 ng/egg

[a] NC: Mothers' were not feather clipped, C: Mothers' were feather clipped in order to reduce postnatal provision rate.

Table 5
Effect of egg corticosterone elevation pre-incubation on behaviour.

Behavioural traits	Effect	Species	Age of testing	Reference	Injection (site and amount)	
Fearfulness						
Tonic immobility						
- *Duration*	=	Yellow legged gull	0–2 days	Rubolini et al. (2005)	Albumin	15 ng/egg
	=, ↑ (handled)	Chicken	4 weeks	Janczak et al. (2007b)	Albumin	5.5 ng/ml
Avoidance of humans	↑	Chicken	2 weeks	Janczak et al. (2006)	Albumin	0.6 μg/egg
Imprinting	↓	Chicken	2 days	Nordgreen et al. (2006)	Albumin	0.6 μg/egg
Competitive ability						
Begging intensity	↓	Yellow legged gull	Hatchling	Rubolini et al. (2005)	Albumin	15 ng/egg
	↑	European starling	Hatchling	Love and Williams (2008b)	Yolk	12.8 ng/g
Begging duration	=	Yellow legged gull	Hatchling	Rubolini et al. (2005)	Albumin	15 ng/egg
	↓♂,=♀	European starling	Hatchling	Love and Williams (2008b)	Yolk	12.8 ng/g
Competing for object	↓	Chicken	4 weeks	Janczak et al. (2006)	Albumin	0.6 μg/egg
Competing for food	=	Chicken	5 weeks	Janczak et al. (2007b)	Albumin	5.5 ng/ml
Motivation/mobility						
Cross wall to access food	↓	Chicken	2 weeks	Janczak et al. (2006)	Albumin	0.6 μg/egg
Flight performance	↑	European starling	21 days	Chin et al. (2009)	Yolk	12.8 ng/g

Table 6
Effect of late prenatal exposure to corticosterone on physiology.

Physiological traits	Effect	Species	Age of testing	Reference	Amount injected	
Growth						
Hatching mass	=	Chicken		Lay and Wilson (2002)	E16	60 ng/egg
	↓	Chicken		Rodricks et al. (2006)	E10-E14	0.2–0.3 nmol/egg
Post hatching mass	=	Chicken	100–130 days	Lay and Wilson (2002)	E16	60 ng/egg
Endocrinology						
Baseline corticosterone	=	Chicken	14 days	Lay and Wilson (2002)	E16	60 ng/egg
	↑	Chicken	Hatching	Rodricks et al. (2006)	E10-E14	0.2–0.3 nmol/egg
HPA-axis response	=/=	Chicken	14 days/11 weeks	Lay and Wilson (2002)	E16	60 ng/egg
Visual pathway lateralization	↓	Chicken	2 days	Rogers and Deng (2005)	E18	60 μg/egg
Secondary sex ratio	=	Chicken	Hatching	Lay and Wilson (2002)	E16	60 ng/egg

E: Embryonic age in days

symmetry in tarsus length was decreased, which is interpreted as a disturbance of the normal developmental progress (see section on FA above; Eriksen et al., 2003).

Baseline CORT was not affected (Hayward et al., 2006; Love and Williams, 2008a) but the HPA response to a challenge was down-regulated in female Japanese quails (Hayward et al., 2006) and in European Starlings of both sexes (Love and Williams, 2008a), which is in contrast to the effects seen when CORT in the mothers' circulation was elevated (see Section 3.1). Finally, the cellular immune reaction to PHA but not the antibody response to a vaccine was down-regulated in semi-precocial gulls (Rubolini et al., 2005) while in the altricial starling the immune response to PHA was up regulated in males offspring but down regulated in female offspring (Love and Williams, 2008b). Interestingly, effects of prenatal CORT exposure on the cellular immunity was dependent on the quality of the postnatal environment (mothers were wing clipped or received sham treatment) and this interaction between the pre-and postnatal environment was different for sons and daughters, resulting in a complex interaction (Love and Williams, 2008b).

The fitness consequence of hatching from eggs injected with CORT is difficult to assess. Most of the effects, such as reduced growth, immunity, plumage development and tarsus length symmetry in offspring exposed to elevated concentrations may indicate lower offspring fitness. However, we are aware of only one study that looked at the fitness consequences in the wild, (European starling, Love and Williams, 2008a), finding higher early mortality in male than female offspring from injected eggs. This is in line with a stronger impairment of growth on male compared to

Table 7
Effect of late prenatal exposure to corticosterone on behaviour.

Behavioural traits	Effect	Species	Age of testing	Reference	Amount injected	
Anxiety						
Open field	=	Chicken	7–9 days	Lay and Wilson (2002)	E16	60 ng/egg
	↑	Chicken	5 days	Freire et al. (2006)	E18	60 μg/egg
Cognition						
Memory	↑	Chicken	1 day	Sui et al., 1997	E19–21	60 ng/egg
	↓	Chicken	1 day	Rodricks et al. (2006)	E10–14	0.2 nmol/egg
Latency to detect predator	↑	Chicken	8–9 days	Freire et al., 2006	E18	60 μg/egg
Dominance (♂)	↓	Chicken	16 weeks	Lay and Wilson (2002)	E16	60 ng/egg

E: Embryonic age in days

female offspring as mentioned above. Interesting, this sex specific mortality did only occur when the mothers were handicapped during rearing by feather clipping. Love and Williams (2008a) argued that this adjustment in brood size and sex ratio might have provided a better match between the mothers rearing capacity and the brood's demands, since feather clipping the mothers would reduce provision to the nestling and female nestlings would be less expensive to rear than sons. This argument found some support when looking at the mother's body mass during the subsequent brood rearing period where it was found that previously feather clipped females, which had raised offspring from CORT treated eggs earlier in the season, lost less weight than previously feather clipped females that had raised control offspring. This indicates that matching the offspring's prenatal environment to a certain postnatal environment might be beneficial for the mother's long-term fitness.

In conclusion, prenatal exposure to elevated levels of CORT shows similar effects on offspring growth and secondary sex ratio as maternal stress. However, contrary to maternal stress, prenatal exposure to elevated CORT leads to a reduction in HPA-axis activity and shows no clear effect on immunity.

4.2. Effect of egg CORT elevation pre-incubation on behaviour

Fearfulness and competitiveness, two of the main behavioural traits assessed in offspring of stressed mothers, have also been tested in birds from CORT injected eggs. In one study no effect of the egg treatment on tonic immobility was found (semi-precocial gulls, Rubolini et al., 2005). In the other study (domestic chickens, Janczak et al., 2006), chicks showed increased avoidance behaviour to humans. Interestingly, the same study found that if chicks from CORT treated eggs were exposed to handling they showed increased fearfulness in a tonic immobility test compared to handled control birds, while no difference was found between the two treatment groups if they were not exposed to handling. This indicates that there might be some kind of clue in the postnatal environment that triggers the effects induced by the prenatal environment. If this is indeed the case it could imply some kind of safety strategy, preventing a certain outcome of the prenatal environment when the postnatal environment does not necessitate the CORT induced phenotypic adjustment. When stressed in adulthood, prenatally stressed rats exhibit a long list of phenotypic changes (prolonged adrenocortical stress response, disturbed circadian rhythm of heart rate, temperature and physical activity as well as increased adrenal weight) that are not evident without the postnatal stimulation (reviewed by Mastorci et al., 2009).

Similar to maternal stress studies, birds from CORT injected eggs were less competitive in a competition test (Janczak et al., 2006) although no difference was found in a food competition test (Janczak et al., 2007b), while begging intensity was affected in opposite directions in the two studies that tested this (*decreased* semi-precocial gull, Rubolini et al., 2005; *increased* altricial starling, Love and Williams, 2008b). Mobility of young birds exposed to elevated levels of prenatal CORT has also been tested, either by looking at chickens ability to cross a wall to access food (Janczak et al., 2006) or by assessing European starlings' flight performance around the time of fledging (Chin et al., 2009). Again, the findings in the altricial starling were opposite to those in the precocial chicken, since prenatal CORT exposure decreased mobility in chickens whereas it increased mobility (at least in terms of flight potential) in European starlings. Finally, the egg injections seem to impair filial imprinting (Nordgreen et al., 2006), suggesting cognitive impairment that has also been found in mammalian studies (Section 2).

In conclusion, there is some preliminary evidence that preincubation injection of CORT induces the same effect on the chick's postnatal fearfulness and ability to compete for food as maternal stress. Begging intensity and mobility have not been assessed in maternal stress studies and results between egg injection studies on altricial and precocial species show inconsistency.

4.3. Challenging the biological validity of egg CORT injection pre-incubation

Injecting CORT into freshly laid eggs has been suggested as a way of mimicking variation in prenatal exposure to maternal stress. However, the biological relevance of these studies might be disputed. First of all as mentioned above, egg CORT concentration might not always be affected by the mother's plasma CORT levels (Janczak et al., 2007b; Cook et al., 2009). Secondly, due to cross-reactions of gestagens in the immunoassays (Rettenbacher et al., 2009), the actual CORT concentrations in egg yolk and albumin might have been overestimated and, as these measurements were used to calculate treatment dosages, CORT levels might not have been manipulated within the physiological range. Although these studies were performed on domesticated poultry, CORT levels in the yolk of wild Great tits after column separation were extremely low as well (Groothuis et al., 2008). Thirdly, when testosterone and CORT dissolved in oil are injected into the yolk of chicken eggs, the oil droplet (with the hormone) concentrated near the area where the embryo develops and 6 days into incubation the hormone is still not evenly distributed in the egg (von Engelhardt et al., 2009). This procedure might therefore lead to the embryo being exposed to pharmacological levels of the hormone and challenges the use of oil-hormone injection in studies as a way of mimicking hormone exposure within the physiological range (von Engelhardt et al., 2009). Based on these 3 points, caution is advised when interpreting the effects of such injection studies. Furthermore, the facts that hormones injected into an egg does not spread quickly in the whole egg (von Engelhardt et al., 2009), suggest that timing and concentration of CORT exposure depends on whether the injection is made into the yolk or the albumin of the egg.

4.4. Injecting eggs with CORT during incubation

A handful of studies have looked at the effects of injecting chicken eggs with CORT during incubation at a time when the embryo has already gone trough a major part of its prenatal development (Tables 6 and 7, discussed in the next section). The presence of glucocorticoids in the blood of the chick embryo has been confirmed already around the 10th day of incubation (Tona et al., 2005). The HPA-axis in this species is functional around the 14th day of incubation (total incubation time is 21 days; Freeman, 1974) and at this stage, corticosterone and cortisol are present in equal amounts (reviewed by Jenkins and Porter, 2004; Kalliecharan and Hall, 1974). Most studies injected eggs between day 10 and day 18 of incubation and thereby exposed the embryo to elevated CORT during the second half of incubation when the embryo itself is capable of producing glucocorticoids. Only one study injected eggs at the very end of incubation between day 19 and 21.

Such late injections would be ecologically relevant in case either maternal CORT is still present in the egg at this stage, or if maternal stress modulates embryonic CORT production. As discussed in Section 4.3, the first possibility is unlikely, because CORT levels in the egg might be very low at this time, due to enzymatic conversion by either the maternal (follicle) or embryonic (yolk sac membranes) tissues. The second possibility is much more likely since stressed mothers may alter incubation behaviour or the HPA axis of the embryo that in turn would affect CORT production of the embryo. Female European starlings exposed to a stressor during incuba-

tion left the nest more often (Cyr et al., 2007) which can lower incubation temperature, and thereby slow embryonic development (Lyon and Montgomerie, 1985; Deeming and Ferguson, 1991; Nuechterlein and Buitron, 2002; Martin et al., 2007) and male penguins equipped with transponders rotated their eggs more often than males without transponders, which correlated with higher post hatch mortality in their offspring (Beaulieu et al., 2010). Several studies have measured HPA-axis response, after ACTH injection or after inflicting pain in embryos incubated under different conditions (Wise and Frye, 1973; Hall, 1977; Tona et al., 2005), but to our knowledge only two studies have looked at embryonic CORT production in relation to incubation conditions (Moraes et al., 2004; Piestun et al., 2009). In both studies the embryos CORT response to increased incubation temperatures (in an industrial incubator) were assessed around mid-incubation and around hatching time. Although incubation temperature did affect the offspring's CORT production in both studies, the direction of the results was inconsistent. It is therefore not possible based on the current literature to say to what extent and in which direction maternal stress during incubation affects embryonic CORT production.

4.4.1. *Effect of late prenatal exposure to CORT on physiology and behaviour*

Late embryonic exposure to elevated levels of CORT can potentially affect the physiology (Table 6) and behaviour (Table 7) of birds. There is some indication that CORT treatment late in incubation can reduce hatching mass (Rodricks et al., 2006; but see Lay and Wilson, 2002). In contrast to injection before incubation, there is no evidence that injection during the incubation period affects post hatching growth or the HPA response (Lay and Wilson, 2002) while it might elevate basal levels of CORT (Rodricks et al., 2006, but see Lay and Wilson, 2002). Also in contrast to early injections, the secondary sex ratio was not affected (Lay and Wilson, 2002). Reduced asymmetry in the visual pathway has been reported in chicks from CORT treated eggs. Brain asymmetries are widespread within the animal kingdom and are supposed to have important adaptive value, as demonstrated on the lateralization in the visual system of chickens (Vallortigara and Rogers, 2005). Reduction in cerebral asymmetry may thus be detrimental and this reduction has been reported in prenatally stressed mammals (reviewed by Weinstock, 2001). The increased latency to detect a predator in chicks from CORT injected eggs may be related to the decrease in lateralization of the visual pathway, as it has been found that chicks showing less strong visual lateralization take longer to detect a predator in a dual task (Freire et al., 2006).

Despite the lacking evidence for affecting the HPA axis, Lay and Wilson (2002) reported increased fearfulness in chickens from CORT injected eggs, although this was not found in the same species by Freire et al. (2006). Prenatal CORT exposure during incubation has been shown to affect memory in birds (Sui et al., 1997; Rodricks et al., 2006) and decrease dominance in male birds (Lay and Wilson, 2002). The former two studies tested the ability of one day old chicks to discriminate between normal beads and beads coated with a bitter tasting substance based on the colour of the beads. The results between the two studies are inconsistent which might be due to the timing of CORT treatment. In one study eggs were treated with CORT around day 10–14 of embryonic development and in this study a decrease in memory was found, while in the other study eggs were treated just prior to hatching around day 19–21 and here memory increased in the chicks.

Injecting eggs with CORT during incubation affects offspring's growth in a similar way as preincubation injection with CORT and maternal stress, and anxiety levels seem to be affected in the same direction as by maternal stress. While memory has not been assessed in maternal stress or preincubation injection studies, the reduced dominance in males might be comparable to the reduced competitiveness reported in offspring of stressed mothers and birds from eggs injected with CORT prior to incubation.

5. Conclusion

As indicated in Section 2, the mammalian embryo seems more sensitive to CORT exposure in the second half of pregnancy. The use of egg injections before and during incubation provides a model to test the sensitivity of the embryo in different stages on development. Intriguingly, the bird studies do not show clear evidence that further developed embryos are more sensitive to CORT. However, the ecological relevance of these studies, especially the pre-incubation treatment, needs further validation. In any case, most of the effects seem detrimental for fitness.

6. General discussion and suggestions for future research

6.1. *Main findings*

It is evident from the current literature that elevated plasma CORT levels in female birds during egg production, as well as CORT treatment of the egg, can induce a variety of alterations in the phenotype of the offspring of these eggs in both behaviour and physiology which have also been found in mammalian species. A substantial part of the studies reported such effects in birds long after hatching or even in adulthood, showing that some of these effects are long lasting. The described effects might not all be independent, since changes in one trait might subsequently change another trait, such as impaired or catch-up growth being causally related to lower immunocompetence. If all traits are linked independently to maternal stress, this would allow a greater diversity of phenotypes to evolve since selection pressure could work independently on each trait. However, linkage of traits or sex specific effects may constrain such evolution (Groothuis and Schwabl, 2008).

So far, studies on the effects of maternal stress in avian offspring are scarce and show a lot of inconsistencies. Reasons for these inconsistencies have already been discussed in Section 3.3. The most consistent finding is a tendency for maternal stress to impair growth. Remarkably, this effect is less consistent among mammalian species (see Section 2). Given the suggestion that maternal CORT is hardly transferred to the egg, the avian studies may be helpful in answering the question to what extent the effects on the mammalian offspring are caused by impaired foetal nutrition or increased CORT exposure.

So far, most studies have relied on egg mass to see if maternal CORT affects the offspring's prenatal nutrition. Since diet has been shown to affect the fatty acid composition of yolk lipids in chicken eggs (Milinsk et al., 2003) and stress hormones affect bird's metabolism (Spencer and Verhulst, 2008) it seems likely that egg yolk composition is affected by maternal stress too. Fatty acids are important for an animal's health and prenatal fatty acid exposure has been shown to promote several neurological functions and support foetal development of the brain, with subsequent effects on the animal's postnatal cognitive ability (reviewed by Cohen et al., 2005). More qualitative analyses of the eggs' albumin and yolk with regards to lipid and protein composition are therefore needed in order to investigate whether or not maternal CORT only affects the quantity (egg size) or if it also affects the quality of nutrition and to what extent this has an impact on the chick.

Since there is evidence that maternal CORT elevation affects levels of gonadal steroids in the egg, this may be an avenue for further research in mammals as well. In relation to this, several effects of maternal stress were found to be sex specific, with females being less sensitive to elevated maternal CORT levels than males. The female biased secondary sex ratio reported when mothers have

elevated CORT during egg formation indicates that females might indeed be better at coping with elevated maternal CORT levels. According to sex allocation theory, parents should invest differently in the two sexes if fitness returns differ between the sexes (Trivers and Willard, 1973). Mothers with elevated CORT might therefore favour producing more females in order to increase their own fitness.

Maternal CORT levels also have the potential to alter the offspring's endocrine system indicated by the increased HPA-axis response and elevated baseline testosterone. Increased HPA-axis response is often seen in mammals exposed to gestational stress. Health conditions have been the main topic when looking at effects of maternal stress in mammals. In bird studies, possible effects of maternal CORT on the offspring's health have been evaluated by measuring the offspring's antibody and T-cell mediated response to an immunochallenge. In birds, maternal CORT seems to decrease their antibody response, and like growth and HPA-axis activity, these effects can be sex dependent. Increased fearfulness and anxiety has also often been observed in offspring of stressed mammalian mothers. Although there is some indication in birds that maternal stress increases fearfulness and anxiety, reduced fearfulness or no effect of maternal CORT levels have also been reported.

A flourishing field in the study of energetics and aging in mammals and birds alike is that of oxidative stress. There is evidence that steroid hormones, immune activation, metabolic rate and growth increase the production of free radicals that induce DNA damage and ultimately reduce fitness (Alonso-Alvarez et al., 2007; Costantini et al., 2010b). We like to encourage studies integrating this field with that of the consequences of maternal stress for offspring.

6.2. Some methodological considerations and advantages of the avian model

In mammals, the effects of maternal CORT levels during gestation depend on the timing and duration of CORT elevation and this might explain many of the inconsistencies between studies. The use of CORT injections in egg during different stages of incubation would be an appropriate tool to investigate sensitive windows for maternal stress. Indeed, the studies of egg injections before and after onset of incubation showed partly different results although the number of studies for a reliable comparison is low. However, this approach requires that, more information is available concerning (1) the transfer of maternal CORT to the egg and (2) variations in embryonic CORT production in relation to maternal stress.

The latter is also relevant for another reason: Although it has not reliably been proven yet that the effects of maternal CORT are mediated via a direct transfer of plasma CORT to the egg, elevated maternal CORT might still affect prenatal CORT exposure, if elevated maternal CORT leads indirectly to an elevated production of CORT by the embryo itself. This might occur either because of a change in egg composition (other steroid hormones or nutrition value), or due to a change in maternal incubation pattern, two things that both potentially can affect embryonic CORT secretion.

Not only measurement and manipulation of egg CORT levels, but also manipulation of maternal CORT levels is problematic. In most studies on birds so far, maternal CORT has been elevated artificially mainly via CORT implants. Implants often lead to an immediate high peak in plasma CORT levels followed by a decline that quickly brings plasma concentrations back to baseline, probably due to corticosteroid-binding globulin (CBG) (Muller et al., submiitted for publication). This transport protein binds a certain percentage of plasma glucocorticoids with high affinity A different method of elevating plasma CORT should be considered in future experiments in order to better mimic natural patterns of CORT secretion. This could for example be done by elevating the female's plasma CORT concentrations in small peaks during the day e.g. by CORT administration via food (Muller et al., submiitted for publication).

The incubation phase has not received a lot of attention within the field of maternal stress in birds. As mentioned earlier, incubation conditions can affect mortality and HPA axis responses in the chicks. The quality of incubation might be just as important as the quality of the egg, but so far no studies have looked at incubation behaviour in female birds with elevated CORT levels and how that might affect the offspring later in life. Different cells and tissues are sensitive at different times, so the effects of incubation could have distinct effects depending not only on the quality of incubation but also on the timing of the female's changes in incubation behaviour. It could be argued that to some extent maternal stress during incubation in birds might be more comparable to studies on maternal stress in mammals during pregnancy than maternal stress in birds during egg production, since only in the first case is the embryo exposed to fluctuating levels of maternal stress during development in the egg, just like mammalian embryos are in the womb.

For identification of sensitive time windows and comparison with altricial mammals such as rats and humans, we have to realise that so far, precocial birds have been the preferred animal models within the field of maternal stress in birds because in those species, post hatch influences of maternal care can easily be eliminated. In general, the physiological state of altricial hatchlings is less mature than that of precocial hatchlings (Choi et al., 1993). Altriciality in avian embryos is believed to have evolved by chicks hatching significantly earlier in the developmental sequence compared to precocial chicks (Rogers, 1995). As a consequence of this shortened time period for development inside the egg, a considerable amount of neuroendocrine and neural development (cell proliferation, neuronal differentiation, synapse formation and myelination) occurs after hatching, whereas in precocial birds much of this development is accomplished before hatching (Rogers, 1995). The early post-hatching environment might therefore have a bigger impact on the development of altricial bird species and thus they might be more susceptible to maternal stress during their nestling phase than precocial species. In that case the effect is not directly mediated by maternal CORT, but by modulation of parental care (food quality and quantity) via maternal CORT. The advantage of the bird model is that a wide array of species exists with different modes of development and future studies should make more use of this. There are several studies looking at the effects of under-nutrition and CORT manipulation in the chick phase of altricial birds. Some of these studies take long-term effects into account in the framework of sexual selection, such as testing the hypothesis that sexual signalling indicates early developmental conditions (Buchanan et al., 2003; Spencer et al., 2003). Such aspects have, however, not been included in the studies on prenatal stress, but would be a valuable avenue for research in both avian and mammalian models.

The wide array of available bird species, each with its own adaptations to its ecological niche, would also allow for testing species specific adaptations in both maternal programming and buffering against prenatal and postnatal stress factors. Some species might be much better adapted to environmental factors such as extreme temperatures, predation pressure, social pressures, and fluctuations in food or water availability than others and this may yield important insight into mechanisms underlying vulnerability and adaptation to prenatal stress.

Finally, the effect of prenatal stress on the offspring may interact with postnatal conditions, (see Section 3 for examples). For example, if mothers program their offspring for certain stressful post-hatching conditions, and these then do not occur, such a mismatch might increase detrimental effects, or suppress these effects if confirmation of the post hatching stress is needed for the prena-

tal effects to become expressed (see Section 3). Unfortunately, this has hardly received any explicit testing yet.

6.3. Are offspring responses to maternal stress adaptive?

Only recently, studies on maternal stress in mammals and birds have considered the possibility that the phenotypic changes in offspring of stressed mothers might be adapted to a specific postnatal environment. This probably stems from the fact that research on the effects of maternal stress originated from the medical world and has mostly been applied to laboratory animals in order to study potentially pathological outcomes of maternal stress. However, within evolutionary biology, developmental plasticity is often seen as an adaptive response to environmental changes, enabling an organism to better meet the demands of the environment in which it will reside (Gilbert and Epel, 2009). Moreover, maternal effects that were often interpreted as disturbing the normal development are now seen as adaptive mechanisms (Mousseau and Fox, 1998). Therefore, there is currently increased interest in the question to what extent phenotypic changes in the offspring induced by maternal stress are adaptive. The prenatal environment, which is influenced by the mother, could potentially signal the conditions of the future environment to the embryo, thereby enabling an adaptive development of certain traits. Bertin et al. (2008) showed that quails hatching from eggs that have been produced while the female was exposed to humans were less fearful towards humans as adults compared to offspring of mothers that were not exposed to humans during egg laying. Natt et al. (2009) found that brain modifications and altered feeding behaviour caused by an unpredictable feeding regime in both female and male chickens could also be detected in their offspring even if the offspring were not subjected to unpredictable feeding. These studies indicate that prenatally induced maternal effects at least in some cases relate to the maternal environment and therefore are also most likely adaptations to the same environment for the offspring. To what extent this maternal programming might be adaptive depends on how well the mother can predict the future environment, in other words the degree, timing and predictability of environmental changes.

These considerations might also translate into more applied settings. For example, commercially bred fowl is incubated, hatched, raised and housed under highly artificial conditions. If a correlation exists between the composition of the egg produced by a stressed female and her incubation behaviour or her own environment, then the use of an artificial incubator or deviating rearing conditions might create a miss-match that affects the offspring's phenotype in a detrimental way.

As mentioned in Section 1, the effects of stress might be dependent on the intensity of the stressor. The hormetic model proposes that the fitness response to a stressor is curve linear with fitness initially increasing with increased stress exposure, while declining at higher stress exposure (Costantini et al., 2010a). The early mild exposure to stress may then prime the animal to deal with higher levels of stress later in life, or may even enhance fitness at all adult stress levels, even in the case of no stress (depending on the cost of the priming process itself). The fitness of an animal might therefore not only depend on how well it's current environment matches it's mothers environment but also on the degree of stress they experienced during development. An example of this (suggested by Costantini et al., 2010a) is the 'optimal developmental temperature' (Zamudio et al., 1995; Huey & Berrigan, 1996) where it is found that animals reared under conditions of mild heat stress will later in life out-perform animals reared at either higher temperatures or at control temperatures. If mild stress early in life increases an animal's fitness, then that animal might out perform control animals in any type of stressful environment

While it is important to keep the concept of hormetic processes in mind when applying stressors to animals both prenatally and postnatally, it is often unclear whether all phenotypic traits abide by hormetic responses and when or how long these responses occur (Costantini et al., 2010a).

Studying maternal stress from an adaptive perspective requires testing whether offspring of stressed mothers cope better with stressful environments than offspring from non-stressed mothers (for a complete design of testing adaptive hormone-mediated maternal effects see Groothuis and von Engelhardt, 2005). Such studies should also address the potential consequences of a mismatch between programming by the mother and the actual postnatal condition of the offspring, as well as the possibility that only confirmation by the offspring of the level of the relevant stressor in the postnatal environment might express the effect of maternal stress in the offspring.

If the effects of maternal stress are adaptive adjustments to the offspring's phenotype, then a more natural setting (environment) with a wild bird species might be more likely to reveal such phenotypic changes as being adaptive than studies using highly selected strains under artificial housing conditions. Also, since many different stressors would evoke a CORT response, the mother may only be able to predict more specifically the offspring's environment and communicate information to the offspring by changing other factors of the prenatal environment than only CORT (see Table 3). Indeed we showed that a physiological stress response involves other hormones and physiological changes in the offspring than just an elevation of plasma CORT. Therefore, testing functional consequences of prenatal maternal stress requires more studies where the mothers and offspring are exposed to a natural stressor instead of only an elevation of CORT concentrations. These types of studies would also provide an opportunity to look at possible long-term fitness cost for the mother herself, and not just for the offspring, similar to the so far unique study of Love and Williams (2008b). This would provide more insight into possible strategies applied by the mother to increase her own fitness both in the short run with her current brood and in the long run via subsequent broods.

The latter points to the fact that a strategy maximizing fitness of the mother might not maximize fitness of all her offspring and could potentially create a parent-offspring conflict (Trivers, 1974). However, the developing embryo might be able to counteract the strategies that the mother applies prenatally if these are not beneficial for the embryo (Carere and Balthazart, 2007; Groothuis and Schwabl, 2008). Studies on prenatal steroid exposure in chickens and turtles have demonstrated that the developing embryo in the egg has some control over its exposure to steroids of maternal origin, by metabolising these to inactive forms (Paitz and Bowden, 2008; von Engelhardt et al., 2009). Embryonic metabolism and uptake of hormones during incubation needs more attention within the field of prenatal stress since it would provide insight into how much control the embryo has over its prenatal environment and what kind of strategies it uses.

6.4. Transgenerational effects beyond the F1 generation and possible mechanisms

There are numerous examples of transgenerational epigenetic inheritance in animals ranging from nematodes, fruit flies and locusts to foxes, rodents and humans (Gilbert and Epel, 2009). In many of these studies, DNA methylation has been described as the 'genetic action' whereby effects get passed on from one generation to the next. DNA-methylation is one of the most important and best studied mechanisms of silencing genes. DNA silencing has become especially important in explaining how an organism can use the environment to establish a phenotype and then trans-

mit that phenotype stably across several generations (Gilbert and Epel, 2009). DNA-silencing and transgenerational effects within the field of maternal stress still remain to be investigated. In order for these effects to be inherited, such exposure must induce either stable chromosomal alterations caused by the same consistent changes in the embryonic environment in subsequent generations (Seckl, 2004) or involve epigenetic modifications that are maintained through germ cell maturation (Jirtle and Skinner, 2007). Germ-line dependent epigenetic can originate from both parents (Rakyan and Beck, 2006) and opens up for the possibility of prenatal influence of paternal stress affecting the offspring's phenotype in addition to effects induced by alteration in incubation behaviour.

Naguib and Gil (2005) showed that in zebra finches body size in nestlings and at nutritional independence were affected by the brood size in which the mothers were raised. Moreover, such female nestlings produced eggs with less maternal testosterone, thereby most likely affecting the F2 generation as well (Gil et al., 2004) The extent to which effects of maternal stress in birds are projected into more than one generation is still hardly studied and may depend on the predictability of the environment. If both the mother and grandmother grew up in the same type of environment, then this might be an even better predictor for the type of environment that the grand-offspring will grow up in because it indicates environmental stability over more than one generation. Possible evidence for accumulative maternal effects in birds come from the study on great tits (Parus major) by Bouwhuis et al. (2010), who found that although maternal age at reproduction did not predict her number of recruits (offspring living until reproductive age) it predicted her number of grand-offspring recruits.

6.5. Concluding remarks

Elevated plasma CORT concentrations in female birds and mammals have the potential to greatly influence their offspring's prenatal development, leading to long-lasting alterations in the offspring's physiology and behaviour postnatally. The underlying pathway of modifying gene expression by maternal CORT are diverse and complex, and may depend on the genes of the mother as well as the genes of the offspring and the offspring environment, but in birds, hardly anything is known on this topic.

While effects of elevated maternal CORT have long been considered purely detrimental for the developing embryo, the idea that effects of maternal stress might be adaptive to the offspring in a certain postnatal environment is starting to get more attention, although research on this is still incomplete, because the postnatal environment is not taken into account.

Likely mediators of these maternal effects are reduced prenatal nutrition and altered steroid hormone exposure, but many questions regarding mechanisms, sensitive periods and potential adaptive effects still remain. By using different bird species with different ecological niches and different modes of development (altricial versus precocial) as model species and altering the experimental design in future experiments we should be able to answer many of these questions and also get insight into beneficial effects of prenatal stress which might explain why natural selection has not selected against the development of traits that can be detrimental for an individual in some contexts but not in others.

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References

Alonso-Alvarez, C., 2006. Manipulation of primary sex-ratio: an updated review. Avian Poult. Biol. Rev. 17, 1–20.
Alonso-Alvarez, C., Bertrand, S., Faivre, B., Chastel, O., Sorci, G., 2007. Testosterone and oxidative stress: the oxidation handicap hypothesis. Proc. R. Soc. Lond. B 274, 819–825.
Amundsen, T., Stokland, J.N., 1990. Egg size and parental quality influence nestling growth in the shag. Auk 107, 410–413.
Andersson, S., Uller, T., Lohmus, M., Sundstrom, F., 2004. Effects of egg yolk testosterone on growth and immunity in a precocial bird. J. Evol. Biol. 17, 501–505.
Antila, E., Leikola, A., Tahka, S., 1984. Early steroid-metabolism by chick blastoderm invitro. Steroids 43, 315–323.
Arendt, J.D., 1997. Adaptive intrinsic growth rates: An integration across taxa. Q. Rev. Biol. 72, 149–177.
Arnold, T.W., Alisauskas, R.T., Ankney, C.D., 1991. Egg composition of American coots in relation to habitat, year, laying date, clutch size, and supplemental feeding. Auk 108, 532–547.
Beaulieu, M., Thierry, A.M., Handrich, Y., Massemin, S., Le Maho, Y., Ancel, A., 2010. Adverse effects of instrumentation in incubating Adelie penguins *(Pygoscelis adeliae)*. Polar Biol. 33, 485–492.
Bertin, A., Richard-Yris, M.A., Houdelier, C., Lumineau, S., Mostl, E., Kuchar, A., Hirschenhauser, K., Kotrschal, K., 2008. Habituation to humans affects yolk steroid levels and offspring phenotype in quail. Horm. Behav. 54, 396–402.
Bonier, F., Martin, P.R., Wingfield, J.C., 2007. Maternal corticosteroids influence primary offspring sex ratio in a free-ranging passerine bird. Behav. Ecol. 18, 1045–1050.
Bouwhuis, S., Charmantier, A., Velhulst, S., Sheldon, B.C., 2010. Trans-generational effects on ageing in a wild bird population. J. Evol. Biol. 23, 636–642.
Buchanan, K.L., Spencer, K.A., Goldsmith, A.R., Catchpole, C.K., 2003. Song as an honest signal of past developmental stress in the European starling (*Sturnus vulgaris*). Proc. Biol. Sci. 270, 1149–1156.
Cadby, C.D., Jones, S.M., Wapstra, E., 2010. Are increased concentrations of maternal corticosterone adaptive to offspring? A test using a placentotrophic lizard. Funct. Ecol. 24, 409–416.
Calabrese, E.J., Staudenmayer, J.W., Stanek III, E.J., Hoffmann, G.R., 2007. Hormesis and high throughput studies: Crump's analysis lacks credibility. Toxicol. Sci. 98, 602–603.
Carere, C., Balthazart, J., 2007. Sexual versus individual differentiation: the controversial role of avian maternal hormones. Trends Endocrinol. Metab. 18, 73–80.
Carey, C., Rahn, H., Parisi, P., 1980. Calories, water, lipid and yolk in avian eggs. Condor 82, 335–343.
Chader, G.J., Reif-Lehrer, L., 1972. Hormonal effects on the neural retina: Corticoid uptake, specific binding and structural requirements for the induction of glutamine synthetase. Biochim. Biophys. Acta (BBA)—Gen. Subjects 264 (1), 186–196.
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. Proc. R. Soc. B Biol. Sci. 276, 499–505.
Choi, I., Ricklefs, R.E., Shea, R.E., 1993. Skeletal muscle growth, enzyme activities and the development of thermogenesis: a comparison between altricial and precocial birds. Physiol. Zool. 66, 455–473.
Chung, S., Son, G.H., Park, S.H., Park, E., Lee, K.H., Geum, D., Kim, K., 2005. Differential adaptive responses to chronic stress of maternally stressed male mice offspring. Endocrinology 146, 3202–3210.
Cohen, J.T., Bellinger, D.C., Connor, W.E., Shaywitz, B.A., 2005. A quantitative analysis of prenatal intake of n-3 polyunsaturated fatty acids and cognitive development. Am. J. Prev. Med. 29, 366–374.
Cook, N.J., Renema, R., Wilkinson, C., Schaefer, A.L., 2009. Comparisons among serum, egg albumin and yolk concentrations of corticosterone as biomarkers of basal and stimulated adrenocortical activity of laying hens. Br. Poult. Sci. 50, 620–633.
Costantini, D., Metcalfe, N.B., Monagan, P., 2010a. Ethological processes in a hormetic framework. Ecol. Lett. 13, 1435–1447.
Costantini, D., Rowe, M., Butler, M.W., McGraw, K.J., 2010b. From molecules to living systems: historical and contemporary issues in oxidative stress and antioxidant ecology. Funct. Ecol. 24, 950–959.
Cottrell, E.C., Seckl, J.R., 2009. Prenatal stress, glucocorticoids and the programming of adult disease. Front. Behav. Neurosci. 3, 19.
Cyr, N.E., Earle, K., Tam, C., Romero, L.M., 2007. The effect of chronic psychological stress on corticosterone, plasma metabolites, and immune responsiveness in European starlings. Gen. Comp. Endocrinol. 154, 59–66.
D'mello, A.P., Liu, Y., 2006. Effects of maternal immobilization stress on birth weight and glucose homeostasis in the offspring. Psychoneuroendocrinology 31, 395–406.
Davis, K.A., Schmidt, J.B., Doescher, R.M., Satterlee, D.G., 2008. Fear responses of offspring from divergent quail stress response line hens treated with corticosterone during egg formation. Poult. Sci. 87, 1303–1313.
de la Cruz, L.F., Illera, M., Mataix, F.J., 1987. Developmental changes induced by glucocorticoids treatment in breeder quail (*Coturnix coturnix japonica*). Horm. Metab. Res. 19, 101–104.
Deeming, D.C., Ferguson, M.W.J., 1991. Egg turning during incubation has no effect upon the growth of embryos of alligator-Mississippiensis. Acta Zool. 72, 125–128.
Downing, J.A., Bryden, W.L., 2008. Determination of corticosterone concentrations in egg albumen: A non-invasive indicator of stress in laying hens. Physiol. Behav. 95, 381–387.

Drake, A.J., Walker, B.R., Seckl, J.R., 2005. Intergenerational consequences of fetal programming by in utero exposure to glucocorticoids in rats. Am. J. Physiol. Regul. Integr. Comp. Physiol. 288, 34–38.
Drake, A.J., Tang, J.I., Nyirenda, M.J., 2007. Mechanisms underlying the role of glucocorticoids in the early life programming of adult disease. Clin. Sci. (Lond.) 113, 219–232.
Durant, S.E., Hepp, G.R., Moore, I.T., Hopkins, B.C., Hopkins, W.A., 2010. Slight differences in incubation temperature affect early growth and stress endocrinology of wood duck *(Aix sponsa)* ducklings. J. Exp. Biol. 213, 45–51.
Eriksen, M.S., Haug, A., Torjesen, P.A., Bakken, M., 2003. Prenatal exposure to corticosterone impairs embryonic development and increases fluctuating asymmetry in chickens (*Gallus gallus domesticus*). Br. Poult. Sci. 44, 690–697.
Eriksen, M.S., Bakken, M., Espmark, A., Braastad, B.O., Salte, R., 2006. Prespawning stress in farmed Atlantic salmon *Salmo salar*: maternal cortisol exposure and hyperthermia during embryonic development affect offspring survival, growth and incidence of malformations. J. Fish Biol. 69, 114–129.
Erisman, S., Carnes, M., Takahashi, L.K., Lent, S.J., 1990. The effects of stress on plasma ACTH and corticosterone in young and aging pregnant rats and their fetuses. Life Sci. 47, 1527–1533.
Finkler, M.S., Van Orman, J.B., Sotherland, P.R., 1998. Experimental manipulation of egg quality in chickens: influence of albumen and yolk on the size and body composition of near-term embryos in a precocial bird. J. Comp. Physiol. B 168, 17–24.
Fisher, M.O., Nager, R.G., Monaghan, P., 2006. Compensatory growth impairs adult cognitive performance. PLoS. Biol. 4, 1462–1466.
Fowden, A.L., Li, J., Forhead, A.J., 1998. Glucocorticoids and the preparation for life after birth: are there long term consequences of the life insurance? Proc. Nutr. Soc. 57, 113–122.
Freeman, B.M., 1974. Hormones in development. In: Freeman, B.M., Vince, M.V. (Eds.), Development of the Avian Embryo. Chapman and Hall, London, pp. 208–235.
Freire, R., van Dort, S., Rogers, L.J., 2006. Pre- and post-hatching effects of corticosterone treatment on behavior of the domestic chick. Horm. Behav. 49, 157–165.
Gil, D., Heim, C., Bulmer, E., Rocha, M., Puerta, M., Naguib, M., 2004. Negative effects of early developmental stress on yolk testosterone levels in a passerine bird. J. Exp. Biol. 207, 2215–2220.
Gil, D., 2008. Hormones in avian eggs: Physiology, ecology and behavior. Adv. Study Behav. 38, 337–398.
Gilbert, A.B., Perry, M.M., Waddington, D., Hardie, M.A., 1983. Role of atresia in establishing the follicular hierarchy in the ovary of the domestic hen (*Gallus domesticus*). J. Reprod. Fertil. 69, 221–227.
Gilbert, S.F., Epel, D., 2009. Ecological Developmental Biology: Integrating Epigenetics, Medicine, and Evolution. Sinauer Associates, Inc, Massachusetts.
Gitau, R., Fisk, N.M., Teixeira, J.M., Cameron, A., Glover, V., 2001. Fetal hypothalamic-pituitary-adrenal stress responses to invasive procedures are independent of maternal responses. J. Clin. Endocrinol. Metab. 86, 104–109.
Gluckman, P.D., Hanson, M.A., 2004. The developmental origins of the metabolic syndrome. Trends Endocrinol. Metab. 15, 183–187.
Gluckman, P.D., Hanson, M.A., Spencer, H.G., 2005. Predictive adaptive responses and human evolution. Trends Ecol. Evol. 20, 527–533.
Grau, C.R., 1976. Ring structure of avian egg-yolk. Poult. Sci. 55, 1418–1422.
Groothuis, T.G., von Engelhardt, N., 2005. Investigating maternal hormones in avian eggs: measurement, manipulation, and interpretation. Ann. N. Y. Acad. Sci. 1046, 168–180.
Groothuis, T.G., Muller, W., von Engelhardt, N., Carere, C., Eising, C., 2005. Maternal hormones as a tool to adjust offspring phenotype in avian species. Neurosci. Biobehav. Rev. 29, 329–352.
Groothuis, T.G., Schwabl, H., 2008. Hormone-mediated maternal effects in birds: mechanisms matter but what do we know of them? Philos. Trans. R. Soc. Lond. B Biol. Sci. 363, 1647–1661.
Groothuis, T.G., Carere, C., Lipar, J., Drent, P.J., Schwabl, H., 2008. Selection on personality in a songbird affects maternal hormone levels tuned to its effect on timing of reproduction. Biol. Lett. 4, 465–467.
Hall, B.K., 1977. Thallium-induced achondroplasia in chicken embryos and the concept of critical periods during development. Teratology 15, 1–15.
Hayward, L.S., Wingfield, J.C., 2004. Maternal corticosterone is transferred to avian yolk and may alter offspring growth and adult phenotype. Gen. Comp. Endocrinol. 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. Gen. Comp. Endocrinol. 146, 144–148.
Hill, W.L., 1993. Importance of prenatal nutrition to the development of a precocial chick. Dev. Psychobiol. 26, 237–249.
Huey, R.B., Berrigan, D., 1996. Testing evolutionary hypotheses of acclimation. In: Johnston, I.A., Bennett, A.F. (Eds.), Animals and Temperature: Phenotypic and Evolutionary Adaptation. SEB Seminar Series. Cambridge University Press, Cambridge, U.K, pp. 205–238.
Janczak, A.M., Braastad, B.O., Bakken, M., 2006. Behavioural effects of embryonic exposure to corticosterone in chickens. Appl. Anim. Behav. Sci. 96, 69–82.
Janczak, A.M., Torjesen, P., Palme, R., Bakken, M., 2007a. Effects of stress in hens on the behaviour of their offspring. Appl. Anim. Behav. Sci. 107, 66–77.
Janczak, A.M., Heikkilae, M., Valros, A., Torjesen, P., Andersen, I.L., Bakken, M., 2007b. Effects of embryonic corticosterone exposure and post-hatch handling on tonic immobility and willingness to compete in chicks. Appl. Anim. Behav. Sci. 107, 275–286.
Jarvis, S., Moinard, C., Robson, S.K., Baxter, E., Ormandy, E., Douglas, A.J., Seckl, J.R., Russell, J.A., Lawrence, A.B., 2006. Programming the offspring of the pig by prenatal social stress: neuroendocrine activity and behaviour. Horm. Behav. 49, 68–80.
Jenkins, S.A., Porter, T.E., 2004. Ontogeny of the hypothalamo-pituitary-adrenocortical axis in the chicken embryo: a review. Domest. Anim. Endocrinol. 26, 267–275.
Jirtle, R.L., Skinner, M.K., 2007. Environmental epigenomics and disease susceptibility. Nat. Rev. Genet. 8, 253–262.
Jones, R.B., 1986. Tonic immobility in the domestic-fowl—a descriptive profile. Appl. Anim. Behav. Sci. 15, 182.
Jones, R.B., 1989. Chronic stressors. Tonic immobility and leukocytic responses in the domestic-fowl. Physiol. Behav. 46, 439–442.
Kaiser, S., Sachser, N., 2005. The effects of prenatal social stress on behaviour: mechanisms and function. Neurosci. Biobehav. Rev. 29, 283–294.
Kalimi, M., 1984. Glucocorticoid receptors – from developing to aging—A review. Mech. Ageing Dev. 24, 129–138.
Kalliecharan, R., Hall, B.K., 1974. A developmental study of the levels of progesterone, corticosterone, cortisol, and cortisone circulating in plasma of chick embryos. Gen. Comp. Endocrinol. 24, 364–372.
Kanitz, E., Otten, W., Tuchscherer, M., Manteuffel, G., 2003. Effects of prenatal stress on corticosteroid receptors and monoamine concentrations in limbic areas of suckling piglets *(Sus scrofa)* at different ages. J. Vet. Med. A Physiol. Pathol. Clin. Med. 50, 132–139.
Kapoor, A., Petropoulos, S., Matthews, S.G., 2008. Fetal programming of hypothalamic-pituitary-adrenal (HPA) axis function and behavior by synthetic glucocorticoids. Brain Res. Rev. 57, 586–595.
Katz, A., Oyama, R.K., Feng, N., Chen, X., Schlinger, B.A., 2010. 11beta-hydroxysteroid dehydrogenase type 2 in zebra finch brain and peripheral tissues. Gen. Comp. Endocrinol. 166, 600–605.
Klusonova, P., Kucka, M., Miksik, I., Bryndova, J., Pacha, J., 2008. Chicken 11 beta-hydroxysteroid dehydrogenase type 2: Partial cloning and tissue distribution. Steroids 73, 348–355.
Konishi, M., Emlen, S.T., Ricklefs, R.E., Wingfield, J.C., 1989. Contributions of bird studies to biology. Science 246, 465–472.
Korte, S.M., Koolhaas, J.M., Wingfield, J.C., McEwen, B.S., 2005. The Darwinian concept of stress: benefits of allostatis and costs of allostatic load and the trade-offs in health and disease. Neurosci. Biobehav. Rev. 29, 3–38.
Kritchevsky, D., Kirk, M.R., 1951. Radioactive eggs. II: Distribution of radioactivity in the yolks. Proc. Soc. Exp. Biol. Med. 78, 200–202.
Lay Jr., D.C., Wilson, M.E., 2002. Development of the chicken as a model for prenatal stress. J. Anim. Sci. 80, 1954–1961.
Lerner, I.M., 1954. Genetic Homeostasis. John Wiley and Sons, New York, NY, USA.
Levitz, M., 1966. Conjugation and transfer of fetal-placental steroid hormones. J. Clin. Endocrinol. Metab. 26, 773–777.
Liggins, G.C., Howie, R.N., 1972. Controlled trial of antepartum glucocorticoid treatment for prevention of respiratory distress syndrome in premature infants. Pediatrics 50, 515–525.
Lippman, M.E., Wiggert, B.O., Chader, G.J., Thompson, E.B., 1974. Glucocorticoid receptors–characteristics, specificity and ontogenesis in embryonic chick neural retina. J. Biol. Chem. 249, 5916–5917.
Lourens, A., van den Brand, H., Heetkamp, M.J.W., Meijerhof, R., Kemp, B., 2007. Effects of eggshell temperature and oxygen concentration on embryo growth and metabolism during incubation. Poult. Sci. 86, 2194–2199.
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. Am. Nat. 166, 751–766.
Love, O.P., Williams, T.D., 2008a. Plasticity in the adrenocortical response of a free-living vertebrate: The role of pre- and post-natal developmental stress. Horm. Behav. 54, 496–505.
Love, O.P., Williams, T.D., 2008b. The adaptive value of stress-induced phenotypes: Effects of maternally derived corticosterone on sex-biased investment, cost of reproduction, and maternal fitness. Am. Nat. 172, E135–E149.
Lyon, B.E., Montgomerie, R.D., 1985. Incubation feeding in snow buntings—female manipulation or indirect male parental care. Behav. Ecol. Sociobiol. 17, 279–284.
Martin, T.E., Auer, S.K., Bassar, R.D., Niklison, A.M., Lloyd, P., 2007. Geographic variation in avian incubation periods and parental influences on embryonic temperature. Evolution 61, 2558–2569.
Mastorci, F., Vicentini, M., Viltart, O., Manghi, M., Graiani, G., Quaini, F., Meerlo, P., Nalivaiko, E., Maccari, S., Sgoifo, A., 2009. Long-term effects of prenatal stress: Changes in adult cardiovascular regulation and sensitivity to stress. Neurosci. Biobehav. Rev. 33, 191–203.
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.
McEwen, B.S., 2000. Allostasis and allostatic load: implications for neuropsychopharmacology. Neuropsychopharmacology 22, 108–124.
Metcalfe, N.B., Monaghan, P., 2001. Compensation for a bad start: grow now, pay later? Trends Ecol. Evol. 16, 254–260.
Meylan, S., Clobert, J., 2005. Is corticosterone-mediated phenotype development adaptive?—Maternal corticosterone treatment enhances survival in male lizards. Horm. Behav. 48, 44–52.
Miki, Y., Nakata, T., Suzuki, T., Darnel, A.D., Moriya, T., Kaneko, C., Hidaka, K., Shiotsu, Y., Kusaka, H., Sasano, H., 2002. Systemic distribution of steroid sulfatase and

estrogen sulfotransferase in human adult and fetal tissues. J. Clin. Endocrinol. Metab. 87, 5760–5768.
Milinsk, M.C., Murakami, A.E., Gomes, S.T.M., Matsushita, M., de Souza, N.E., 2003. Fatty acid profile of egg yolk lipids from hens fed diets rich in n-3 fatty acids. Food Chem. 83, 287–292.
Møller, A.P., Swaddle, J., 1997. Asymmetry, Developmental Stability and Evolution. Oxford University Press, United Kingdom.
Moraes, V.M.B., Malheiros, R.D., Bruggeman, V., Collin, A., Tona, K., Van As, P., Onagbesan, O.M., Buyse, J., Decuypere, E., Macari, M., 2004. The effect of timing of thermal conditioning during incubation on embryo physiological parameters and its relationship to thermotolerance in adult broiler chickens. J. Therm. Biol. 29, 55–61.
Mousseau, T.A., Fox, C.W., 1998. Maternal Effects. Oxford University Press, New York.
Muller, W., Groothuis, T.G., Kasprzik, A., Dijkstra, C., Alatalo, R.V., Siitari, H., 2005. Prenatal androgen exposure modulates cellular and humoral immune function of black-headed gull chicks. Proc. Biol. Sci. 272, 1971–1977.
Murphy, B.E., Clark, S.J., Donald, I.R., Pinsky, M., Vedady, D., 1974. Conversion of maternal cortisol to cortisone during placental transfer to the human fetus. Am. J. Obstet. Gynecol. 118, 538–541.
Nager, R.G., 2006. The challenges of making eggs. Ardea 94, 323–346.
Naguib, M., Gil, D., 2005. Transgenerational effects on body size caused by early developmental stress in zebra finches. Biol. Lett. 1, 95–97.
Natt, D., Lindqvist, N., Stranneheim, H., Lundeberg, J., Torjesen, P.A., Jensen, P., 2009. Inheritance of acquired behaviour adaptations and brain gene expression in chickens. PLoS One 4, e6405.
Navara, K.J., Mendonca, M.T., 2008. Yolk androgens as pleiotropic mediators of physiological processes: A mechanistic review. Comp. Biochem. Physiol., Part A Mol. Integr. Physiol. 150, 378–386.
Nisbet, I.C.T., 1978. Dependence of fledging success on egg-size, parental performance and egg-composition among common and roseate terns, Sterna-Hirundo and S-Dougallii. Ibis 120, 207–215.
Nordgreen, J., Janczak, A.M., Bakken, M., 2006. Effects of prenatal exposure to corticosterone on filial imprinting in the domestic chick. *Gallus gallus domesticus*. Anim. Behav. 72, 1217–1228.
Nuechterlein, G.L., Buitron, D., 2002. Nocturnal egg neglect and prolonged incubation in the Red-necked Grebe. Waterbirds 25, 485–491.
Nuyt, A.M., 2008. Mechanisms underlying developmental programming of elevated blood pressure and vascular dysfunction: evidence from human studies and experimental animal models. Clin. Sci. 114, 1–17.
O'Regan, D., Welberg, L.L., Holmes, M.C., Seckl, J.R., 2001. Glucocorticoid programming of pituitary-adrenal function: mechanisms and physiological consequences. Semin. Neonatol. 4, 319–329.
Ohkawa, T., Rohde, W., Takeshita, S., Dorner, G., Arai, K., Okinaga, S., 1991. Effect of an acute maternal stress on the fetal hypothalamo-pituitary-adrenal system in late gestational life of the rat. Exp. Clin. Endocrinol. 98, 123–129.
Ozanne, S.E., Nicholas, H.C., 2005. Poor fetal growth followed by rapid postnatal catch-up growth leads to premature death. Mech. Ageing Dev. 126, 852–854.
Paitz, R.T., Bowden, R.M., 2008. A proposed role of the sulfotransferase/sulfatase pathway in modulating yolk steroid effects. Integr. Comp. Biol. 48, 419–427.
Parsons, I.C., 1970. The metabolism of testosterone by early chick embryonic blastoderm. Steroids 16, 59–65.
Parsons, P.A., 1990. Fluctuating asymmetry: an epigenetic measure of stress. Biol. Rev. Camb. Philos. Soc. 65, 131–145.
Piestun, Y., Halevy, O., Yahav, S., 2009. Thermal manipulations of broiler embryos–the effect on thermoregulation and development during embryogenesis. Poult. Sci. 88, 2677–2688.
Pike, T.W., Petrie, M., 2006. Experimental evidence that corticosterone affects offspring sex ratios in quail. Proc. R. Soc. Lond. B: Biol. Sci. 273, 1093–1098.
Polak, M., Trivers, R., 1994. The science of symmetry in biology. Trends Ecol. Evol. 9, 122–124.
Raberg, L., Grahn, M., Hasselquist, D., Svensson, E., 1998. On the adaptive significance of stress-induced immunosuppression. Proc. R. Soc. B Biol. Sci. 265, 1637–1641.
Rakyan, V.K., Beck, S., 2006. Epigenetic variation and inheritance in mammals. Curr. Opin. Genet. Dev. 16, 573–577.
Rettenbacher, S., Mostl, E., Hackl, R., Palme, R., 2005. Corticosterone in chicken eggs. Ann. N. Y. Acad. Sci. 1046, 193–203.
Rettenbacher, S., Mostl, E., Groothuis, T.G.G., 2009. Gestagens and glucocorticoids in chicken eggs. Gen. Comp. Endocrinol. 164, 125–129.
Robert, K.A., Vleck, C., Bronikowski, A.M., 2009. The effects of maternal corticosterone levels on offspring behavior in fast- and slow-growth garter snakes (*Thamnophis elegans*). Horm. Behav. 55, 24–32.
Roudybush, T.E., Grau, C.R., Petersen, M.R., Ainley, D.G., Hirsch, K.V., Gilman, A.P., Patten, S.M., 1979. Yolk formation in some Charadriiform birds. Condor 81 (3), 293–298.
Rodricks, C.L., Miller, S.L., Jenkin, G., Gibbs, M.E., 2006. The role of corticosterone in prehatch-induced memory deficits in chicks. Brain Res. 1123, 34–41.
Rogers, L.J., 1995. The Development of Brain and Behaviour in the Chicken. CAB International, Oxon, UK.
Rogers, L.J., Deng, C., 2005. Corticosterone treatment of the chick embryo affects light-stimulated development of the thalamofugal visual pathway. Behav. Brain Res. 159, 63–71.
Romanoff, A.L., Romanoff, A.J., 1949. The Avian Egg. John Wiley and Sons Inc., New York.
Rozenboim, I., Tako, E., Gal-Garber, O., Proudman, J.A., Uni, Z., 2007. The effect of heat stress on ovarian function of laying hens. Poult. Sci. 86, 1760–1765.
Rubolini, D., Romano, M., Boncoraglio, G., Ferrari, R.P., Martinelli, R., Galeotti, P., Fasola, M., Saino, N., 2005. Effects of elevated egg corticosterone levels on behavior, growth, and immunity of yellow-legged gull *(Larus michahellis)* chicks. Horm. Behav. 47, 592–605.
Salvante, K.G., Williams, T.D., 2003. Effects of corticosterone on the proportion of breeding females, reproductive output and yolk precursor levels. Gen. Comp. Endocrinol. 130, 205–214.
Saino, N., Romano, M., Ferrari, R.P., Martinelli, R., Moller, A.P., 2005. Stressed mothers lay eggs with high corticosterone levels which produce low-quality offspring. J. Exp. Zoolog. A Comp Exp. Biol. 303, 998–1006.
Sapolsky, R.M., Romero, L.M., Munck, A.U., 2000. How do glucocorticoids influence stress responses? Integrating permissive, suppressive, stimulatory, and preparative actions. Endocr. Rev. 21, 55–89.
Sas, B., Domany, G., Gyimothy, I., Kovacsne, K.G., Suth, M., 2006. Influence of the type of management system on corticosterone transfer into eggs in laying hens. Acta Vet. Hung. 54, 343–352.
Satterlee, D.G., Cole, C.A., Castille, S.A., 2007. Maternal corticosterone further reduces the reproductive function of male offspring hatched from eggs laid by quail hens selected for exaggerated adrenocortical stress responsiveness. Poult. Sci. 86, 572–581.
Satterlee, D.G., Hester, A., Leray, K., Schmidt, J.B., 2008. Influences of maternal corticosterone and selection for contrasting adrenocortical responsiveness in Japanese quail on developmental instability of female progeny. Poult. Sci. 87, 1504–1509.
Schmeling, S.K., Nockels, C.F., 1978. Effects of age, sex, and ascorbic-acid ingestion on chicken plasma corticosterone levels. Poult. Sci. 57, 527–533.
Seckl, J.R., 1997. Glucocorticoids, feto-placental 11 beta-hydroxysteroid dehydrogenase type 2, and the early life origins of adult disease. Steroids 62, 89–94.
Seckl, J.R., 2004. Prenatal glucocorticoids and long-term programming. Eur. J. Endocrinol. 151, U49–U62.
Shanks, N., Lightman, S.L., 2001. The maternal-neonatal neuro-immune interface: Are there long-term implications for inflammatory or stress-related disease? J. Clin. Invest. 108, 1567–1573.
Sloboda, D.M., Challis, J.R., Moss, T.J., Newnham, J.P., 2005. Synthetic glucocorticoids: antenatal administration and long-term implications. Curr. Pharm. Des. 11, 1459–1472.
Sotherland, P.R., Rahn, H., 1987. On the composition of bird eggs. Condor 89, 48–65.
Spencer, K.A., Buchanan, K.L., Goldsmith, A.R., Catchpole, C.K., 2003. Song as an honest signal of developmental stress in the zebra finch (Taeniopygia guttata). Horm. Behav. 44, 132–139.
Spencer, K.A., Verhulst, S., 2008. Post-natal exposure to corticosterone affects standard metabolic rate in the zebra finch (*Taeniopygia guttata*). Gen. Comp. Endocrinol. 159, 250–256.
Stamps, J.A., Groothuis, T.G.G., 2010. Developmental perspectives on personality: implications for ecological and evolutionary studies of individual differencese. Philos. Trans. R. Soc. B. 365, 4029–4041.
Stokland, J.N., Amundsen, T., 1988. Initial size hierarchy in broods of the shag—Relative significance of egg size and hatching asynchrony. Auk 105, 308–315.
Sui, N., Sandi, C., Rose, S.P., 1997. Interactions of corticosterone and embryonic light deprivation on memory retention in day-old chicks. Brain Res. Dev. Brain Res. 101, 269–272.
Tegethoff, M., Pryce, C., Meinlschmidt, G., 2009. Effects of intrauterine exposure to synthetic glucocorticoids on fetal, newborn, and infant hypothalamic-pituitary-adrenal axis function in humans: a systematic review. Endocr. Rev. 30, 753–789.
Thomson, D.L., 1999. Intraindividual variance in trait size and the analysis of developmental instability. Anim. Behav. 57, 731–734.
Tona, K., Onagbesan, O., Bruggeman, V., Mertens, K., Decuypere, E., 2005. Effects of turning duration during incubation on embryo growth, utilization of albumen, and stress regulation. Poult. Sci. 84, 315–320.
Trivers, R.L., Willard, D.E., 1973. Natural selection of parental ability to vary the sex ratio of offspring. Science 179, 90–92.
Trivers, R.L., 1974. Parent–offspring conflict. Am. Zool. 14, 249–264.
Turner, B.B., 1997. Influence of gonadal steroids on brain corticosteroid receptors: a minireview. Neurochem. Res. 22, 1275–1385.
Vallortigara, G., Rogers, L.J., 2005. Survival with an asymmetrical brain: Advantages and disadvantages of cerebral lateralization. Behav. Brain Sci. 28, 575–589.
Viltart, O., Vanbesien-Mailliot, C.C.A., 2007. Impact of prenatal stress on neuroendocrine programming. Sci. World J. 7, 1493–1537.
von Engelhardt, N., Henriksen, R., Groothuis, T.G.G., 2009. Steroids in chicken egg yolk: Metabolism and uptake during early embryonic development. Gen. Comp. Endocrinol. 163, 175–183.
Von Engelhardt, N., Groothuis, T.G.G., 2010. Maternal hormones in avian eggs. In: Norris, D.O., Lopez, K.H. (Eds.), Hormones and Reproduction in Vertebrates, vol. 4. Elsevier, Amstrerdam, NL, pp. 91–128.
Waddington, C.H., 1942. Canalization of development and the inheritance of acquired characters. Nature 150, 563–565.
Ward, I.L., Weisz, J., 1984. Differential effects of maternal stress on circulating levels of corticosterone, progesterone, and testosterone in male and female rat fetuses and their mothers. Endocrinology 114, 1635–1644.
Weinstock, M., 2001. Alterations induced by gestational stress in brain morphology and behaviour of the offspring. Progr. Neurobiol. 65, 427–451.
Weinstock, M., 2005. The portential influence of maternal stress hormones on development and mental health of the offspring. Brain Behav. Immun. 19 (4), 296–308.
Weinstock, M., 2008. The long-term behavioural consequences of prenatal stress. Neurosci. Biobehav. Rev. 32, 1073–1086.

Welberg, L.A., Seckl, J.R., Holmes, M.C., 2001. Prenatal glucocorticoid programming of brain corticosteroid receptors and corticotrophin-releasing hormone: possible implications for behaviour. Neuroscience 104, 71–79.
Wilckens, T., 1995. Glucocorticoid and immune function: physiological relevance and pathogenic potential of hormonal dysfunction. Trends Pharmacol. Sci. 16, 193–197.
Wingfield, J.C., 2005a. The concept of allostasis: Coping with a capricious environment. J. Mammal. 86, 248–254.
Wingfield, J.C., 2005b. Historical contributions of research on birds to behavioral neuroendocrinology. Horm. Behav. 48, 395–402.
Wise, P.M., Frye, B.E., 1973. Functional development of hypothalamo-hypophyseal-adrenal cortex axis in chick-embryo, *Gallus-Domesticus*. J. Exp. Zool. 185, 277–291.
Zamudio, K.R., Huey, R.B., Crill, W.D., 1995. Bigger isn't always better—body-size, developmental and parental temperature and male territorial success in *Drosophila melanogaster*. Anim. Behav. 49, 671–677.