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Chronic elevation of glucorticoids late in life generates long lasting changes in physiological state without a life history switch

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ABSTRACT

Chronic stressors have profound impacts on phenotypes and life history strategies on the short term, but delayed effects of stress experienced late in life remain poorly investigated in wild populations. Here, we used a combined laboratory and field experiment to test if chronic stress late in life has immediate and delayed effects on physiological and demographic traits in the common lizard, *Zootoca vivipara*. We increased plasma corticosterone levels in adults and yearlings during three weeks of the post-reproductive season. We quantified immediate responses in the laboratory, delayed intra-generational effects in field enclosures one month and one year later during the next reproductive season, and delayed inter-generational effects in the first generation of offspring. Our phenotypic assays included metabolism, immune capacities, lipid metabolism and oxidative stress. Relative to placebos, lizards treated with corticosterone had higher body condition and lower oxidative damages but an increased skin swelling response directly after the manipulation. Delayed responses in field enclosures were of three types. First, we found catch-up growth for body mass such the placebos had similar body conditions one month after the laboratory manipulation. Second, we found persistent differences in oxidative damages during one month but not one year later. Third, during the next reproductive season, corticosterone-treated females had higher levels of plasma triglycerides, whereas corticosterone-treated individuals had a higher skin swelling response. We found no delayed inter-generational effects on demographic traits of offspring. Our study demonstrates the potential for long-lasting physiological consequences of chronic corticosterone enhancement despite no obvious changes in life history.

1. Introduction

Individuals face multiple stressors throughout their life, and behavioural and physiological strategies have therefore evolved to avoid the deleterious effects of these stressors. Among vertebrates, the adrenocortical response, characterized by a rapid rise of glucocorticoid secretion in response to a wide range of stressor stimuli, is one of the most conserved physiological mechanisms for that purpose (Wingfield, 2003). Glucocorticoid secretion after a stressful event induces a cascade of organismal responses that promote immediate survival by reallocating energy from storage to activity (Crespi et al., 2013; Sapolsky et al., 2000). Indeed, glucocorticoids are intimately associated to metabolic activities involved in energy balance (Sapolsky et al., 2000; Solomon et al., 2011), which in turn controls growth, reproduction, and survival (Artacho and Nespolo, 2009; Steyermark, 2002). In addition, glucocorticoids are powerful regulators of immune functions and oxidative stress (Costantini et al., 2011; Dhabhar, 2002; Dhabhar and McEwen, 1997). High chronic levels of plasma glucocorticoid can suppress immune functions (Sapolsky et al., 2000) and have also been associated to oxidative stress increase (Sahin and Gumuslu, 2007). Therefore, chronic stressful events can induce deleterious effects such as immune depression, lower survival or reproduction failures (Crespi et al., 2013).

The ecological relevance of these glucocorticoid effects has been well investigated in both captive and natural populations where energy expenditure, immunity and oxidative stress responses can be potentially important fitness related traits (Alonso-Alvarez et al., 2006). Physiological and demographic responses are generally measured during or

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right after the stressful event and can be referred to as "immediate" effects of chronic elevation of glucocorticoids. Yet, the life of individuals is made out of a series of critical events or life stages, and there is accumulating evidence that environmental variation at a given life stage can impact the following life stages through delayed, intra-generational effects as well as the following generations through inter-generational effects (Beckerman et al., 2002; Meylan et al., 2012). Thus, prolonged stressful events, such as chronic food restriction, can have long lasting effects throughout the entire life of the individual and may shift its life history strategy. In particular, chronic elevation of glucocorticoids may have organizational effects and thus could influence ontogenic trajectories on the long-term (Schoech et al., 2011). For example, Spencer and collaborators (Spencer and Verhulst, 2007; Spencer et al., 2005) chronically supplemented nestlings of zebra finch (*Taeniopygia guttata*) with corticosterone (one of the two major glucocorticoid with cortisol in birds, amphibians, reptiles and mammals) and found immediate negative effects on growth as well as delayed effects on song characteristics in adults. Exposure to elevated glucocorticoids early in life can also disrupt HPA axis regulation (Kitaysky et al., 2005) and has profound, well-known long-term effects on the physiology, behaviour, and life history (Blas et al., 2007; Dufty et al., 2002; Matthews, 2002; Meylan and Clobert, 2005). These impacts of glucocorticoid can carry over across generations through maternal effects (Catalani et al., 2000; Khan et al., 2016).

Glucocorticoid secretion can induce phenotypic plasticity at adulthood as well (Dufty et al., 2002), but its long lasting, delayed effects have been little investigated so far in late life stages. Here, we used common lizards (*Zootoca vivipara*) as a model system to investigate for the first time the joint immediate and delayed physiological and demographic effects of a prolonged corticosterone increase late in life. Immediate effects of prolonged high secretion of corticosterone in adult common lizards include changes in resting and activity metabolism, immune capacities, oxidative stress, and behaviours such as food consumption, locomotor activity and basking (Cote et al., 2006; Meylan and Clobert, 2005; Meylan et al., 2010). Moreover, a prolonged corticosterone administration increases the future survival of adult males but not females suggesting sex-specific long lasting, delayed effects (Cote et al., 2006). In this viviparous species, increased corticosterone secretion right during gestation further changes the morphology, behavioural activity and dispersal strategy of juveniles at birth (de Fraipont et al., 1999; Meylan et al., 2002, 2004), but can also influence their growth and survival later in life (Meylan and Clobert, 2005). However, we do not know if increased corticosterone secretion some months before the gestation period can cause maternal effects later in life.

To quantify immediate and delayed intra-generational and inter-generational effects, we used a three-stage experimental design where we first exposed yearlings and adults to a chronic corticosterone exposure during the summer post-reproductive season in the laboratory. We next released all lizards in outdoor populations until the next reproductive season, and then followed for an additional season their first generation of offspring. In yearlings and adults, we measured repeatedly four sets of physiological parameters (standard metabolic rate, immune capacities, oxidative stress and plasmatic triglyceride concentration) directly after the treatment, one month later in the field and one year later in the field to identify most relevant components of the adrenocortical response. Consequences on life history were examined by quantifying reproductive performances, growth, survival rate and the intergenerational effects on the first generation of offspring. At the end of the laboratory manipulation, we expected an increase of baseline corticosterone, as well as of triglyceride concentration (Karatsoreos et al., 2010; Peckett et al., 2011), oxidative stress (Cote et al., 2010b), and leanness (Cote et al., 2006, 2010a). In contrast, we predicted no change in immune response in accordance with previous work (Meylan et al., 2010) but sex-dependent changes of metabolic rates (Cote et al., 2010b; Meylan et al., 2010). Since previous works have shown sex-specific delayed effects on survival in adults (Cote et al., 2006), we expected different long-lasting responses between sexes. If chronic corticosterone exposure increases maintenance costs, we predicted a long-term decrease of immune capacities and an increase of oxidative stress, plasmatic triglyceride concentrations and baseline corticosterone (Cote et al., 2006; McEwen and Wingfield, 2003; Romero et al., 2009). Moreover, since the energetic costs of maintenance change between age classes, sex and reproductive cycles (Massot et al., 2011; McEwen and Wingfield, 2003), we expected stronger delayed effects during the reproductive period, one year after the manipulation, than one month after the treatment because energy demands peek during the reproductive season in both sexes.

2. Materials and methods

2.1. Model species

The lizard *Zootoca vivipara* is a small ovoviparous (adult snout-vent length SVL: 53–77 mm) species inhabiting humid habitats across northern Eurasia. It is characterized by a 3–4 year life expectancy, continuous growth and plastic life history (Le Galliard et al., 2005; Mugabo et al., 2010). Natural populations are structured in three age classes: juveniles (less than one year old), yearlings (between one and two years old) and adults (2 year old or more). In our study site, adult and yearling males start to emerge from hibernation around the beginning of March, followed shortly by juveniles and by adult and yearling females. Mating period starts upon emergence of reproductive females (Bauwens et al., 1989). From June to July, gravid females lay an average clutch of five non-calcified eggs (range 1–13). Offspring hatch shortly after parturition and are immediately autonomous. Lizards enter in hibernation in October.

2.2. Capture and rearing condition

Lizards were captured between 18 and 26 May 2014 in outdoor enclosures (10 × 10 m) at the Centre de Recherche en Ecologie Expérimentale et Prédictive (Saint-Pierre-lès-Nemours, France, 48°17′ N, 2°41′ E). All animals were identified by their unique toe clip code and measured for body size (SVL, ± 0.5 mm) and body mass (± 1 mg). They were then maintained in individual terraria (25 × 15 × 16 cm) with a shelter, peat soil as substrate and opportunities for optimal thermoregulation. We used incandescent light bulbs (25 W) for 9 h/d to ensure a thermal gradient from room temperature at 17–23 °C to 35–38 °C below the bulb during daytime. Room temperature was maintained at 16 °C from 21:00 to 7:30 (night time) and at 25 °C during daytime. We provided lizards with water and food *ad libitum* and kept all individuals under strictly identical conditions until gravid females gave birth. Immediately after parturition, newborns were separated from their mother, marked by toe clipping and measured for their SVL and body mass, and immediately released in an outdoor enclosure.

2.3. Experimental design

We sampled 68 adult and 61 yearling females and 32 adult and 60 yearling males for this experiment. Experiment started when gravid females gave birth (20 June–14 July 2014) and therefore included a balanced sample of post-reproductive females and other age and sex classes. At day 1 of the experiment, lizards from each age and sex class were assigned to a corticosterone (33 adult and 30 yearling females; 16 adult and 30 yearling males) or a placebo group (35 adult and 31 yearling females; 16 adult and 30 yearling males). We subsequently manipulated the circulating levels of corticosterone during 3 weeks using a non-invasive method designed by Meylan et al. (2003). This method increases the baseline corticosterone concentration within the natural range of variation (Meylan et al., 2003). We diluted

corticosterone (Sigma-Aldrich, France, C2505-500 mg 92%, $C_{21}H_{30}O_4$) in commercial sesame oil, which facilitates skin penetration of corticosterone, to reach a final concentration of 3 µg corticosterone for 1 µl of sesame oil. We applied 4.5 µl of corticosterone mixture (corticosterone group) or pure sesame oil (placebo) each evening between 20:00 h and 21:00 local time during 21 days (a duration corresponding to 10% of the yearly activity period). At the start of the experiment, there was no difference in SVL ($\chi^2 = 0.35$, df = 1, P = 0.55) and body mass ($\chi^2 = 0.14$, df = 1, P = 0.70) between treatment groups.

At the end of the laboratory experiment, all lizards were released in 10 outdoor enclosures from 20 July to 6 August. We used the standard set-up and maintenance procedures in each enclosure (Lecomte and Clobert, 1996). We visited all enclosures repeatedly between 2 and 10 September 2014, approximatively one month after release, and attempted to recapture all alive animals. Captured lizards were maintained during 4 days in the laboratory for subsequent measurements (see below) and then released in their capture enclosure. A second visit after the wintering period was done between 18 May and 12 June 2015, approximatively 10 months after release, and captured lizards were again maintained in the laboratory for similar measurements. In addition, all gravid females were maintained until the parturition to assess their reproductive traits. Immediately after parturition, all newborns were separated from their mother, marked by toe clipping and measured for SVL and body mass. Each sibling group was released in one of 10 enclosures (N = 342), and newborns were recaptured in May-June 2016 (N = 70) to measure their size growth and annual survival. The schedule of the experiment is described in Fig. 1.

2.4. Life history data

We monitored the fate of yearlings and adults until May-June 2014 to assess body size and condition, growth, survival and female reproductive performance approximatively one year after the manipulation. We recaptured 164 lizards from the two treatment groups in September 2014 and 107 individuals in May-June 2015. At each time step of the experimental design (pre-experimental, post-experimental, September 2014, and May-June 2015), we sampled blood and measured immuno-competence for all animals and measured whole-organism metabolism for a subset of lizards (see below). Body growth rates were calculated as the change in SVL between two captures divided by the time interval. We subtracted the number of inactive days spent in hibernation for the growth rate whenever needed. Hibernation is assumed to be from end of October to beginning of March. We estimated annual survival probabilities assuming that capture probability was very close to 1 in May-June, where we make a strong effort to attempt to recapture all live lizards (Le Galliard et al., 2005). To assess reproductive performance of females, we counted live new-borns, dead new-borns and aborted or unfertilized eggs of each clutch. Parturition date, total fecundity (live, dead and aborted newborns), fit fecundity (live newborns) and offspring characteristics (sex, SVL, body mass) were recorded.

2.5. Blood sample and plasma measurements

Blood samples (40–80 µl whole blood) were taken from the infra-

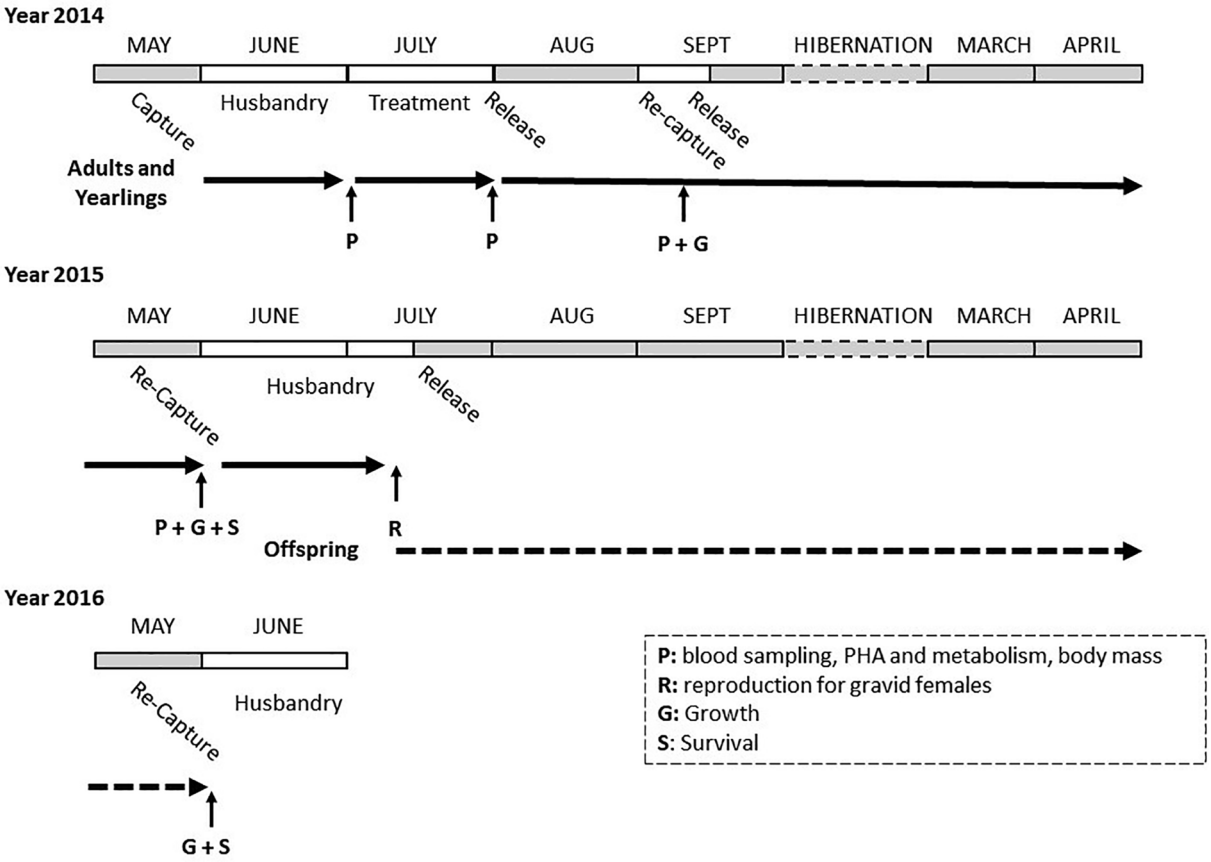

Fig. 1. Diagram representing the timing of the experiment over the 3 years of the study. Lizards were captured in outdoor conditions, maintained in the laboratory for acclimation and subsequently manipulated for corticosterone elevation during three weeks. Pre- and post-experimental physiological measurements (indicated by P in the figure) were performed in the laboratory. Lizards then alternated life in outdoor conditions (indicated by grey rectangle) and laboratory (white rectangle) for the purpose of subsequent measurements. After recaptures in September 2014 and May-June 2015, lizards were kept in the laboratory for 2 days for acclimation and subsequently measured. We measured reproductive parameters (R), growth (G) and survival (S). In May 2016, we measured growth and survival on juveniles born from the experimental individuals.

Table 1
Sample sizes for each age class (AD: adults, YLG: yearlings) and sex per hormonal treatment during each session for each physiological trait. We used exactly the same samples for pre- and immediate post-experiment measurements. The samples in September 2014 and May-June 2015 were dependent of the recapture collection.

	Pre-experiment (June-July 2014)Post-experiment (July-August 2014)						Session September 2014						Session May-June 2015					
	Control			Corticosterone-treated			Control			Corticosterone-treated			Control			Corticosterone-treated		
	Females		Males	Females		Males	Females		Males	Females		Males	Females		Males	Females		Males
	AD	YLG	AD	AD	YLG	AD	YLG	AD	YLG	AD	YLG	AD	YLG	AD	YLG	AD	YLG	AD	YLG	AD	YLG
Corticosterone	3	3	3	4	5	4	3	4	5	3	6	4	4	5	3	5	0*	6	4	3	2	4
Total	14			16				18				17			14				13			
Oxidative damage	5	9	5	6	10	6	7	6	10	4	10	6	10	4	9	3	4	3	5	4	5	3	3
Total	27			29				30				29				15				15			
Anti-oxidant barrier	5	9	5	6	10	4	7	6	9	4	10	6	9	4	10	3	4	3	5	4	5	3	4
Total	26			27				29				29				15				16			
Triglyceride	3	4	4	5	4	3	5	7	10	4	6	6	13	4	11	3	3	3	5	4	4	2	3
Total	17			17				27				34				14				13			
Swelling response	33	30	16	35	31	16	30	22	24	10	20	24	24	12	25	10	14	4	17	12	18	9	19
Total	109			112				76				85				45				58			
Metabolism	15	15	15	15	15	15	15	8	13	10	9	9	11	8	13	4	10	5	9	5	8	7	9
Total	60			60				40				41				28				29			

orbital sinus using 2–3 20 µl microhematocrit tubes, within 3 min of handling to avoid the handling-induced increase in plasma corticosterone levels (Dauphin-Villemant and Xavier, 1987). Plasma was obtained by centrifugation at 5000 *g* for 3 min of the blood samples and was stored at −20 °C until assay. Because of the low available amount of plasma, the different assays could not be made on the same sample. Thus, plasma extracts were distributed pseudo-randomly in different lots in order to obtain balanced samples for each kind of assay and among treatment, age and sex groups. In general, between 3 and 6 individuals from each age class, sex, and treatment were used to measured corticosterone levels and 3–10 individuals were used to measure triglyceride, anti-oxidant barrier and oxidative damage (see details in Table 1). The same individuals were measured twice before and after the laboratory experiment for the same assay to calculate intra-individual changes during the corticosterone manipulation. Different individuals were randomly sampled for the same assay in outdoor enclosures.

Corticosterone level was measured with a competitive enzyme-immunoassay method using corticosterone EIA (IDS Corticosterone EIA kit, ref AC-14F1, IDS EURL Paris, France) after 1:10 dilution of all samples. This method quantities total plasmatic corticosterone using a polyclonal corticosterone antibody and is based on a colorimetric assay of absorbance at 450 nm. Sensitivity is 0.55 ng/mL. Measurements were highly repeatable (intra-plate repeatability: $n = 63$, $F_{3,60} = 102.61$, $P < 0.001$, $r = 0.89$; inter-plate repeatability: $n = 63$, $F_{16,47} = 51.3$, $P < 0.001$, $r = 0.93$). Levels of circulating triglyceride were measured by colorimetric assays using 2.5 µl of plasma (Triglyceride Colorimetric Assay kit, ref. 10010303, Cayman Chemical, USA). This method quantifies the total triglyceride by using a chain of three enzymatic reactions ending up in hydrogen peroxide production. Sensitivity is 0.5 mg/dL and measurement was highly repeatable (inter-plate repeatability: $n = 24$, $F_{4,20} = 795.48$, $P < 0.001$, $r = 0.99$, intra-plate repeatability: $n = 24$, $F_{2,22} = 728.06$, $P < 0.001$, $r = 0.98$).

To assess oxidative stress in lizards, we used two complementary colorimetric tests. First, we used d-ROMs test (MC003, Diacron International, Via Zircone 8, 58100 Grosseto (GR), Italy) to measure the concentration of reactive oxygen metabolites in 4 µl plasma sample. Second, to assess the anti-oxidant barrier of plasma, we used the OXY-Absorbent test (MC435, Diacron International, Via Zircone 8, 58100 Grosseto (GR), Italy) after 1:100 dilution of 3 µl of plasma. These two tests were also highly repeatable (d-ROMs test: inter-plate repeatability: $n = 16$, $F_{4,12} = 37.53$, $P < 0.001$, $r = 0.91$; intra-plate repeatability: $n = 16$, $F_{2,14} = 46.69$, $P < 0.001$, $r = 0.88$ and OXY test: inter-plate repeatability: $n = 18$, $F_{4,14} = 153.26$, $P < 0.001$, $r = 0.88$; intra-plate repeatability: $n = 18$, $F_{3,15} = 214.96$, $P < 0.001$, $r = 0.98$). Prior to the beginning of the manipulation, there was no difference between treatment groups for corticosterone (Likelihood-ratio tests, $\chi^2 = 0.99$, $df = 1$, $P = 0.32$), triglyceride concentration ($\chi^2 = 0.06$, $df = 1$, $P = 0.81$), oxidative damage ($\chi^2 = 0.09$, $df = 1$, $P = 0.76$) and anti-oxidant barrier capacity ($\chi^2 = 0.15$, $df = 1$, $P = 0.69$).

2.6. Evaluation of immune capacities

Immuno-competence was assessed by measuring skin swelling in response to an injection of a mitogen, the phytohaemagglutinin (PHA). This procedure triggers a local haemagglutination and leukocyte infiltration and involves both adaptive and innate immune components (Martin et al., 2006). This implies that primary responses measured in naive animals may differ from the secondary responses measured in animals already exposed to PHA earlier in their life. In addition, a previous study in this species has shown no correlation between the primary and the secondary swelling responses, but an increase in the swelling response after a first exposure to PHA (Mugabo et al., 2015). In order to avoid biases due to differences between first and subsequent injections, we first injected all animals with a solution of phosphate buffered saline (PBS) containing 2.5 mg/mL of PHA (PHA-M, Sigma-

Aldrich; reference 9008-97-3) in the right posterior leg in order to elicit a primary response. To obtain our subsequent measurements, we then administered a second subcutaneous injection of PHA solution in the right posterior leg and quantified the secondary skin-swelling response. Just before and 12 h after the second injection, we measured the thickness of the right posterior leg using a spessimeter (Mitutoyo, ID-C112, Kanagawa, Japan) with an accuracy of 0.01 mm. We spaced the two measurements by 12 h because this coincides with the greatest swelling response (Mugabo et al., 2015). Secondary swelling response was calculated as the difference in leg thickness between the post- and pre-injection measurements. At the start of the experiment, we did not find difference between treatment groups for swelling response ($\chi^2 = 0.72$, df = 1, P = 0.394).

2.7. Whole-organism metabolic expenditure

We defined at the start of the experiment a sub-sample of 60 males and 60 females from the two age classes to measure repeatedly their resting metabolic rate during the four measurement periods. All individuals were measured during the pre-experiment and post-experiment sessions but only recaptured animals could be measured during the sessions of September 2014 and May-June 2015 (see numbers in Table 1). The resting metabolic rate, or standard metabolic rate (SMR) for ectotherms, is the minimum energetic cost of maintenance estimated in fasting individuals at rest and at a given temperature. Here, we measured the SMR after a fasting period of 3 days to ensure a post-absorptive state (Artacho et al., 2013). Before measurement, lizards were moved in a dark room maintained at 20 °C during 3–4 h and then placed in a metabolic chamber during 1 h at 16 °C before the beginning of the measurements. This temperature was chosen because it is a body temperature where lizards are inactive. All measurements were recorded at night between 08:00 pm and 08:00 am. The CO_2 production was sampled during 40 min for each animal with a multiple-channel, flow-through respirometry system (Qubit Systems, Kingston, ON, Canada) compounded of a CO_2 analyzer (S157) connected to a respirometry software (QS Research). Incoming air flowed through columns of sodalime (Spherasorb, Wokingham, Berkshire, RG41 2RZ, UK) and drierite to remove CO_2 and H_2O, respectively. After the absorbent columns, air was pushed through seven channels of a multiplexer at 150 ml.min^{-1}. Six channels were used for measuring lizards and one channel for the CO_2 reference. Outgoing air was pushed into the CO_2 analyzer at 50 ml.min^{-1}. Metabolic records of CO_2 were processed by a macro program C950 data acquisition software (Qubit systems) in order to transform the ppm measure of CO_2 production in mL per hour, which takes into account the flow rate.

2.8. Statistical analyses

Analyses were performed with R 3.1.0 (R Core Team, 2014, https://www.r-project.org/) using the *lmer* statistical procedure available in the *lme4* package for linear mixed models (Bates et al., 2015) and *lm* procedure from *stats* package for linear models. Analyses of variance procedure were done with the *Anova* procedure from *Car* package (Fox and Weisberg, 2011) All initial models included as fixed factors the effects of treatment group, age class, sex and their first-order interactions. Analyses of corticosterone and triglyceride concentrations, antioxidative-barrier and oxidative damage, swelling response, SMR (CO_2 production) and body mass from the post-experimental session were done by calculating the difference between the post-experimental (after 20 days of treatment application) and the initial measurement and using this as a response variable in a linear model. Data for corticosterone, triglyceride concentrations, antioxidative-barrier, oxidative damage, swelling response and SMR were log-transformed to fit the normality assumption. Because SMR may increase with body mass, we used the mass gain between pre and post experimental session as a covariate, and initial measurement of SVL was also used as covariate in other models.

During the September 2014 session, the choice of plasma samples was made in such a way as to balance the numbers by treatment, sex and age class in order to test their effect (see above). Then, we analysed results from plasma assays with linear mixed models including population identity as a random factor, if necessary after a log-transformation to fit the normality assumption. To assess the change in body mass and SMR, we used the difference between the September and the post-experimental measurements since repeated measures on the same animals were obtained for these traits. In addition, we used SVL as covariate for all traits except body mass change and SMR change where we used change in SVL and body mass as covariates, respectively. The same procedures were used to analyse data collected during the May-June 2015 session. In addition, we analysed SVL growth rate from September 2014 to May-June 2015 with a linear mixed model including the effect of initial SVL to control for growth deceleration with increasing body size and the effect of the date of release to control for potential seasonal changes in growth rates.

Annual survival was analysed with mixed-effect logistic regressions including a logit link and binomial error term. Initial SVL was used as covariate to control for size effect on survival. All adult and yearling females bred during the summer 2015. Parturition date and offspring characteristics (SVL and body condition) were analysed with linear mixed models, whereas total fecundity and fit fecundity were analysed with mixed effect log regressions including a log link and a Poisson error term. Body growth and annual survival of the first generation of offspring were analysed with the same procedures including the mother identity as an additive random effect.

In all cases, parameters of linear mixed models were estimated with the maximum likelihood procedure, whereas a Laplace approximation of the maximum likelihood was used in the case of logistic and log regressions. Fixed effects were tested with Wald χ^2 statistics for mixed models and Fisher tests for linear models. A minimum adequate model was obtained by a backward selection procedure where we removed non-significant terms one by one. Assumptions of normality and homoscedasticity were verified and over-dispersion of logistic and log regression were tested with a Pearsons's chi squares. When a minimum adequate model was found, we used the Tukey's procedure to conduct post hoc tests (pairwise comparisons) with the *lsmeans* package (Lenth, 2016). Results are presented as mean parameter estimates ± standard error or [lower,upper] at 95% confidential interval unless otherwise stated.

3. Results

3.1. Immediate physiological effects

Relative to the placebo, the corticosterone treatment increased significantly plasma corticosterone concentration (Table 2, Fig. 2A) and the skin swelling response (Table 2, Fig. 2C) during the laboratory manipulation, but it did not influence circulating plasma triglyceride concentration (Table 2, Fig. 2B), antioxidant barrier (Table 3, Fig. 3A) and SMR ($F_{1,114} = 0.06$, P = 0.81). In addition, oxidative damages were more important in placebo than in corticosterone treated lizards (Table 3, Fig. 3B). Corticosterone treatment significantly increased body mass change during the laboratory manipulation ($F_{1,207} = 11.94$, $P < 0.001$, Fig. 4A) after controlling for effects of sex ($F_{1,207} = 7.3$, P = 0.007), age class ($F_{1,207} = 227.65$, $P < 0.001$), and initial body mass ($F_{1,207} = 358.74$, $P < 0.001$).

3.2. Delayed physiological and demographical effects

One month after manipulation, baseline corticosterone concentration returned to similar levels between placebo and treatment groups

Table 2
Immediate and delayed (September 2014: one month later and May-June 2015: next year) effects of experimental treatment (corticosterone vs placebo) on plasma corticosterone (A) and triglyceride (B) concentration as well as the swelling response (C), a measure of the inflammatory immune response. Test statistics from a backward elimination procedures are provided and bolded values are significant (< 0.05). Sample size (N) is underlined.

	Factor	Immediate effects			Delayed effects one month				Delayed effects next year			
		F	P	N	χ^2	df	P	N	χ^2	df	P	N
A. Corticosterone concentration ($ng.ml^{-1}$)	Treatments	**F1,27 = 7.75**	**0.01**		0.29	1	0.89		0.54	1	0.46	
	Age	F1,24 = 2.53	0.11		**5.94**	**1**	**0.01**		**8.23**	**1**	**0.004**	
	Sex	F1,25 = 1.4	0.25		**18.92**	**1**	**< 0.001**		**5.29**	**1**	**0.02**	
	SVL	F1,26 = 0.54	0.47		**7.63**	**1**	**0.006**		**4.67**	**1**	**0.03**	
	Initial measurement	**F1,27 = 17.71**	**< 0.001**									
	Age × Treatments	F1,21 = 2.50	0.13		0.03	1	0.87		0.65	1	0.42	
	Sex × Treatments	F1,21 = 0.59	0.45		0.67	1	0.41		0.02	1	0.88	
	Age × Sex	F1,21 = 0.01	0.91	30	0.26	1	0.61	35	0.5	1	0.48	27
B. Triglyceride concentration ($mg.dl^{-1}$)	Treatments	F1,32 = 1.72	0.2		2.45	1	0.11		0.62	1	0.43	
	Age	F1,31 = 0.2	0.66		**4.79**	**1**	**0.03**		3.41	1	0.06	
	Sex	F1,29 = 0.05	0.82		0.44	1	0.5		**22.83**	**1**	**< 0.001**	
	SVL	F1,30 = 0	0.98		0.06	1	0.81		1.16	1	0.28	
	Initial measurement	**F1,32 = 43.5**	**< 0.001**									
	Age × Treatments	F1,26 = 0.03	0.86		0.17	1	0.67		0.77	1	0.38	
	Sex × Treatments	F1,26 = 0.27	0.61		0.53	1	0.47		**7.63**	**1**	**0.006**	
	Age × Sex	F1,26 = 0.53	0.47	34	0.10	1	0.75	61	0.05	1	0.82	27
C. Skin swelling response (mm)	Treatments	**F1,217 = 3.74**	**0.05**		0.05	1	0.83		**5.47**	**1**	**0.02**	
	Age	**F1,217 = 26.39**	**< 0.001**		0.01	1	0.91		1.85	1	0.17	
	Sex	F1,216 = 0.42	0.51		0.18	1	0.67		0.1	1	0.75	
	SVL	F1,214 = 2.66	0.10		**15.42**	**1**	**< 0.001**		**10.08**	**1**	**0.001**	
	Initial measurement	**F1,217 = 277.56**	**< 0.001**		0.87	1	0.35		0.1	1	0.75	
	Age × Treatments	F1,212 = 0.18	0.67		2.55	1	0.11		2.47	1	0.12	
	Sex × Treatments	F1,212 = 1.34	0.25		2.28	1	0.13		3.02	1	0.08	
	Age × Sex	F1,215 = 1.92	0.17	221	0.61	1	0.44	161	0	1	0.99	103

(Fig. 2D), and baseline concentrations were higher in adults and in females after controlling for a negative effect of body size (Table 2). In sharp contrast, we found a delayed effect on triglyceride concentration and swelling response in May-June 2015 but not in September 2014. One year after manipulation, triglyceride concentration was significantly higher in females from the corticosterone group than the placebo (Tukey's contrast = 0.94 ± 0.04, df = 22.48, t = 2.36, adjusted P = 0.03) but not for males (contrast = −0.53 ± 0.37, df = 19, t = −1.43, adjusted P = 0.17). Skin swelling response of the corticosterone treated lizards was significantly higher than in placebos (see Table 2, Fig. 2I). At the same time, we found delayed effects on oxidative damage but not for anti-oxidative barrier (see Fig. 3C-F and Table 3). Oxidative damage was significantly lower in corticosterone treated group than the placebo in September 2014 (Fig. 3D). We did not observe delayed effect of corticosterone treatment on SMR (September 2014: χ^2 = 0.07, df = 1, P = 0.79; May-June 2015: χ^2 = 0.39, df = 1, P = 0.53).

During the time interval between release and September 2014, lizards from the corticosterone treatment gained less body mass than placebos (χ^2 = 9.67, df = 1, P = 0.002, Fig. 4) after controlling for a significant interaction between sex and age (χ^2 = 10.64, df = 1, P = 0.001). There was no difference between treatment groups for size growth between release in 2014 and recapture in May-June 2015 (placebo: 0.016 ± 0.0015 $mm.days^{-1}$, corticosterone: 0.015 ± 0.002 $mm.days^{-1}$; χ^2 = 0.43, df = 1, P = 0.51) after controlling for a negative effect of initial SVL (χ^2 = 200.5, df = 1, P < 0.001) and a sex effect (χ^2 = 254.8, df = 1, P < 0.001). We also found a marginal difference between treatment groups for mass change between September 2014 and May-June 2015 (χ^2 = 3.48, df = 1, P = 0.06), with a slightly lower mass gain in corticosterone treated group.

Estimated annual survival rate was not different between treatment groups (placebo = 0.40 [0.26, 0.56] and corticosterone = 0.52 [0.37, 0.67], χ^2 = 2.61, df = 1, P = 0.11) and between sexes (χ^2 = 2.18, df = 1, P = 0.14). Estimated survival rate of yearling lizards was higher than adults (adults = 0.35 [0.22, 0.50]; yearlings = 0.58 [0.43, 0.71], χ^2 = 3.88, df = 1, P = 0.05). Similarly, we found no delayed effects of corticosterone enhancement on female reproductive traits, including parturition date, number of live offspring and total fecundity (all P > 0.1).

3.3. Inter-generational effects

Juveniles born from corticosterone treated females did not differ from those of placebo females for body size (SVL: χ^2 = 0.54, df = 1, P = 0.46) and body condition at birth (χ^2 = 0.8, df = 1, P = 0.37) after controlling for sexual difference (SVL: χ^2 = 68.81, df = 1, P < 0.001; body condition: χ^2 = 21.97, df = 1, P < 0.001). Estimated annual survival rate of juveniles between 2015 and 2016 was not different between maternal treatment groups (placebo = 0.19 [0.13, 0.27], corticosterone = 0.24 [0.18, 0.32], χ^2 = 0.97, df = 1, P = 0.32). The body size growth rate of juveniles born from corticosterone treated females did not differ from placebos (χ^2 = 0.68, df = 1, P = 0.41) after controlling for the faster growth of females (χ^2 = 3.92, df = 1, p = 0.05) and the decrease of growth rate with birth date (χ^2 = 8.77, df = 1, P = 0.003).

4. Discussion

Our combined laboratory and field experiment evidenced immediate and delayed effects of chronic corticosterone elevation on physiological parameters related to lipid metabolism, immune capacities and oxidative stress, independently of age classes but with some differences between sexes. In addition, body mass increased more rapidly in the laboratory in corticosterone treated lizards, but we later observed compensatory responses in the field with stronger relative body mass change in placebo lizards. In contrast, standard metabolism, survival, reproduction of lizards and the demographic traits of their first generation of offspring were insensitive to the corticosterone

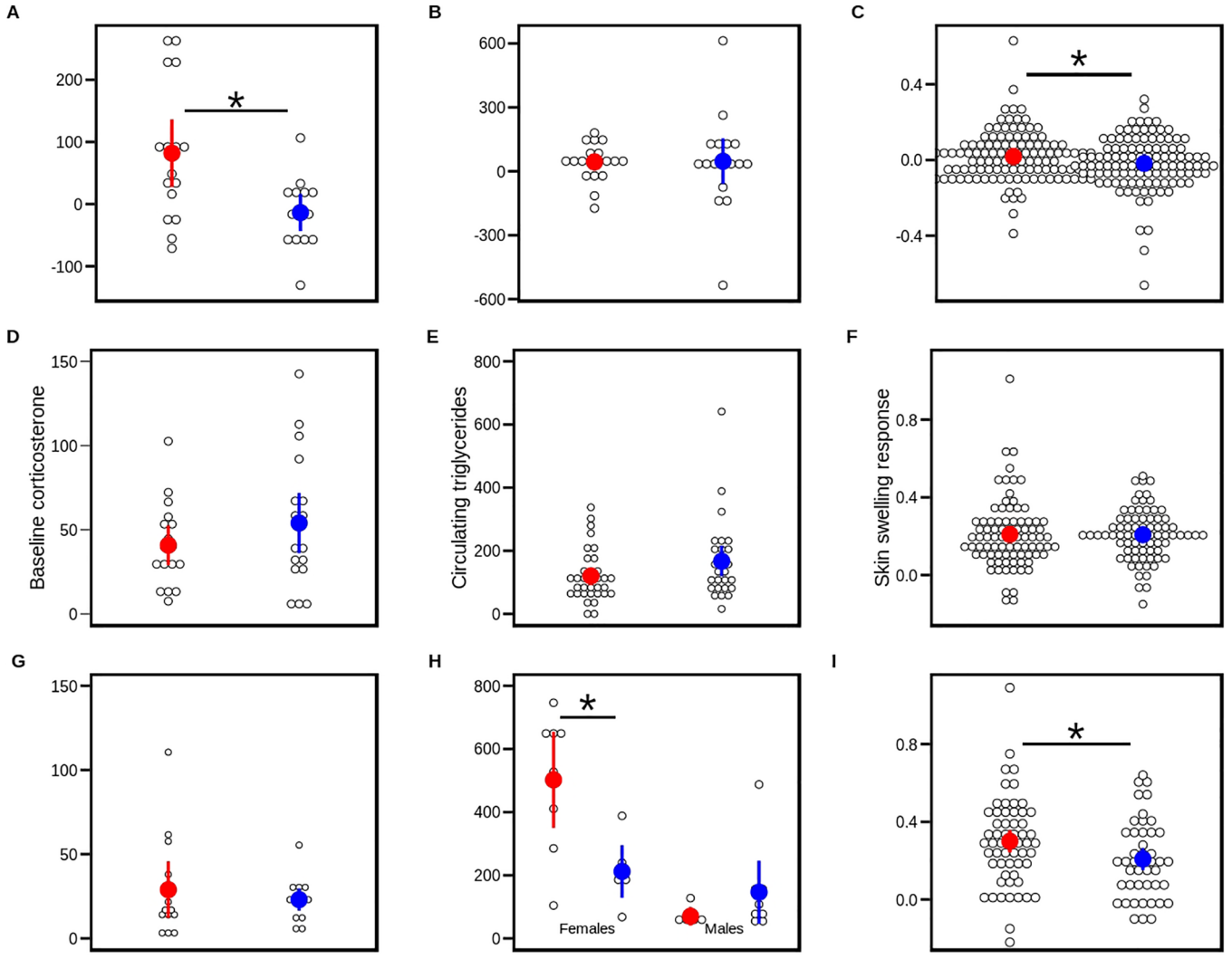

Fig. 2. Immediate effects of corticosterone increase (corticosterone increase: red, placebo: blue) on baseline corticosterone (ng.ml^{-1}), circulating triglycerides (mg.dl^{-1}) and skin swelling response (mm) (A-C) as well as delayed effects one month later (September 2014, D-F) and the next year (May-June 2015, G-I). Panels A-C display the differences between post and pre-experimental values, while panels D-K represent individual scores. Values are presented as means ± 95% confidence intervals and dotplots of raw data per group.

Table 3
Immediate and delayed (September 2014 and May-June 2015) effects of experimental treatment (corticosterone vs placebo) on (A) oxidative damage and (B) anti-oxidant barrier. Test statistics from a backward elimination procedures are provided and bolded values are significant (< 0.05). Sample size (N) is underlined.

	Factor	Immediate effects			Delayed effects one month				Delayed effects next year			
		F	P	N	χ^2	df	P	N	χ^2	df	P	N
A. Oxidative damage (Conc_U)	Treatments	**F1,53 = 6.19**	**0.02**		**3.92**	**1**	**0.05**		0.01	1	0.93	
	Age	F1,51 = 2.38	0.13		1.46	1	0.23		0.27	1	0.60	
	Sex	F1,50 = 1.85	0.18		**5.8**	**1**	**0.02**		3.41	1	0.06	
	SVL	F1,52 = 2.03	0.16		**6.19**	**1**	**0.01**		2.08	1	0.15	
	Initial measurement	**F1,53 = 16.75**	**< 0.001**									
	Age × Treatments	F1,47 = 2.09	0.15		1.73	1	0.19		0.16	1	0.69	
	Sex × Treatments	F1,47 = 0.51	0.36		0.09	1	0.76		0.94	1	0.33	
	Age × Sex	F1,47 = 0.85	0.43	56	1.28	1	0.3	59	1.78	1	0.18	30
B. Anti-oxidant barrier (µl HCLO.ml^{-1})	Treatments	F1,50 = 2.24	0.14		0.16	1	0.69		0.40	1	0.52	
	Age	F1,47 = 0.04	0.84		0.81	1	0.37		0.78	1	0.67	
	Sex	F1,49 = 1.43	0.24		3.47	1	0.06		3.01	1	0.08	
	SVL	F1,48 = 0.7	0.41		0.51	1	0.48		0.18	1	0.67	
	Initial measurement	**F1,50 = 230.04**	**< 0.001**									
	Age × Treatments	F1,45 = 1.16	0.29		3.03	1	0.08		0.73	1	0.39	
	Sex × Treatments	F1,45 = 0.08	0.78		1.1	1	0.29		0.08	1	0.77	
	Age × Sex	F1,45 = 0.67	0.42	53	1.59	1	0.11	58	0.12	1	0.73	31

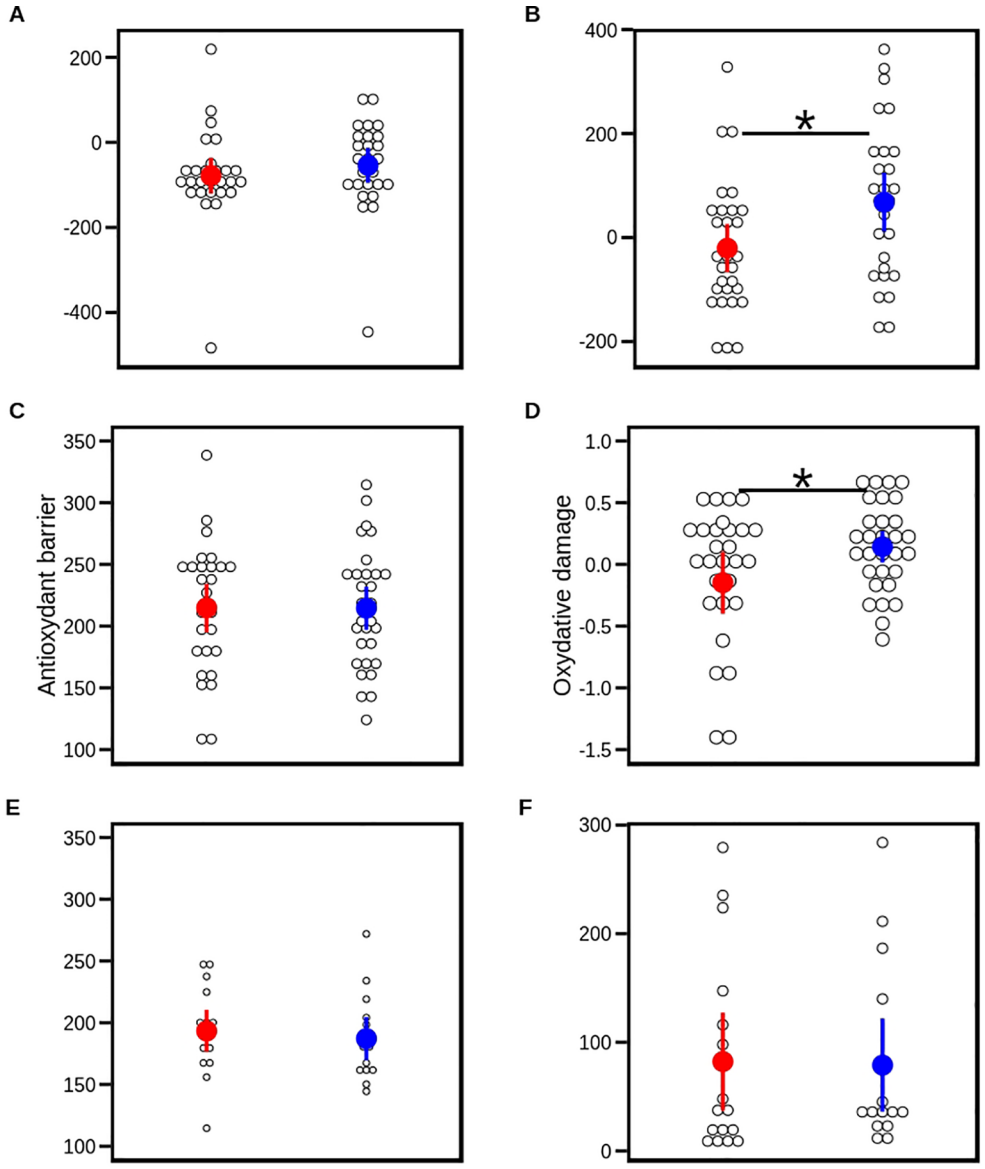

Fig. 3. Immediate effects of corticosterone increase (corticosterone increase: red, placebo: blue) on antioxidant barrier (Conc U) and oxidative damage (µl HCLO.ml^{-1}) (A-B) as well as delayed effects one month later (September 2014, C-D) and the next year (May-June 2015, E-F). Panels A and B represent differences between post and pre-experimental values in the laboratory, while panels C to F represent raw individual values. Values are presented as means ± 95% confidence intervals and dotplots of raw data per group. In panel B, raw data are residuals from a linear regression against body size.

manipulation. Thus, experimental enhancement of corticosterone level, which was used to simulate a chronic stressful event late in life, was a significant factor of physiology and body mass dynamics, but not of the life history strategy.

4.1. Effects on immune and antioxidant capacities

As in previous studies using the same protocol (Cote et al., 2006, 2010b; Meylan et al., 2003), daily inputs of corticosterone for 21 days induced an increase of individual corticosterone level, which was about 3 times higher in the corticosterone group (167.3 ng.ml^{-1} vs. 48.3 ng.ml^{-1} in placebos). An inhibition of the swelling response by the corticosterone treatment was expected given the well-known immunosuppressive actions of the chronic secretion of corticosterone (Berger et al., 2005; Dhabhar and McEwen, 1997; Martin et al., 2005; Sapolsky et al., 2000). Unexpectedly, our chronic corticosterone elevation was instead associated with a higher immune response and less oxidative damage. The increase of swelling response in corticosterone treated lizards did not last in the field one month after the end of the laboratory manipulation; yet, the swelling response measured during the next reproductive season was again higher in corticosterone-treated lizards than in placebos. We speculate that this increased swelling response during the reproduction following corticosterone increase may be adaptive. Indeed, it has been shown that a higher basal level of corticosterone in males resulted an increase in the number of mating attempts, which may expose individuals to more injury or pathogens, thus selecting for higher cellular defences (Gonzalez-Jimena and Fitze, 2012; Richard et al., 2012).

The observed decrease of plasmatic oxidative damage was even more surprising, especially since the treatment did not influence the antioxidant capacity. Chronic application of corticosterone in adult males was previously found to increase oxidative damage under some circumstances, as shown by higher levels of lipid peroxidation in muscular tissues, but it had complex and contrasted effects on antioxidant enzyme activities (Cote et al., 2010b; Meylan et al., 2010). During a chronic stress, oxidative damage is expected to increase

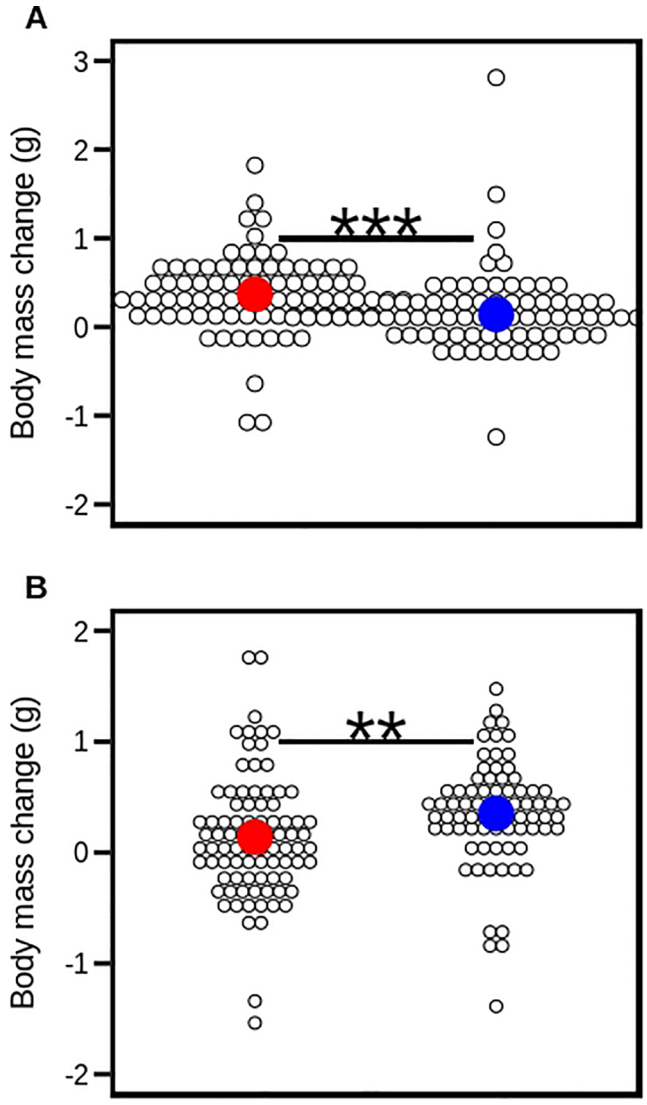

Fig. 4. Immediate (from pre- to post-experimental values in the laboratory, A) and delayed body mass change (one month after the manipulation, B) in lizards from corticosterone increase (red) and placebo (blue) groups. Values are presented as means ± 95% confidence intervals and dotplots of raw data per group.

because higher circulating levels of corticosterone should increase the basal metabolic rate, locomotor activity and foraging behaviour (Costantini et al., 2011). Aerobic metabolism produces reactive oxygen species (ROS), which in turn can result in oxidative damage if ROS generation exceeds antioxidant defences. In our study, the standard metabolic rate of lizards did not change between treatment groups, implying that the decrease of oxidative damage during the laboratory manipulation was not due to changes in basal metabolism. However, we recently demonstrated that the liver mitochondria from corticosterone-treated lizards produced less reactive oxygen species without change in the metabolic rate or oxygen consumption (Voituron et al., 2017). The persistent difference between treatment groups in the field one month after the end of the laboratory manipulation, despite no differences in the immune response, corticosterone concentration or antioxidant barrier, suggests a short-lasting carry-over effect on blood oxidative damage.

4.2. Effects on body mass and metabolism

Although a positive effect of corticosterone enhancement on basal metabolic rate is generally expected, the experimental evidence is rather contradictory and we found no immediate and delayed effects on SMR. In birds, for example, corticosterone elevation has been associated with a reduction of nocturnal metabolism (Buttemer et al., 1991). In contrast, Wikelski et al. (1999) found no apparent relationship between resting metabolic rate and corticosterone levels in white-crowned sparrows (*Zonotrichia leucophrys gambelii*). Moreover, an experimental study in two wild passerine bird species, house sparrows (*Passer domesticus*) and gray catbirds (*Dumetella carolinensis*), demonstrated that the relationship between metabolic rate and corticosterone concentration differed qualitatively between the species (Cohen et al., 2008). In the common lizard, the effect of the corticosterone on metabolism is condition-dependent as well. Indeed, Meylan et al. (2010) found an increase of the SMR after 21 days of corticosterone application in pregnant females; whereas SMR decreased after 10 days of treatment in adult males (Cote et al., 2010a) and did not change in yearlings (Voituron et al., 2017).

Despite the lack of change in whole-organism metabolic expenditure, we observed a significantly higher mass gain in the corticosterone treated group during the laboratory manipulation followed by a higher mass gain from placebo lizards in the field, which altogether indicates a compensatory response. The laboratory result is in contradiction with previous studies (Cote et al., 2006, 2010a) that used other food items (*Pyralis* sp. larva instead of *Acheta domestica*) provided in much smaller quantities (250 mg every 5 days instead of 300–400 mg every 2 days), which are insufficient for sustained body growth in the laboratory. In contrast, our laboratory protocol brought food in excess and allowed for significant size growth like in the field. In the common lizard, a prolonged corticosterone elevation promotes behaviours associated with food intake including exploratory activity, foraging and basking (Cote et al., 2010a). Corticosterone can also induce lipid storage in non-fasted state by activating lipogenesis and adipogenesis (Peckett et al., 2011; Voituron et al., 2017). The body mass gain during the laboratory experiment could thus result from an increase of both food intake and lipid storage. Against the later hypothesis, we however found no difference between treatment groups for plasma triglyceride concentration in the laboratory and one month after the end of the laboratory manipulation.

In the field, the body mass gain in corticosterone treated group was lower in placebo group, and body mass between the two groups was not different one month after the end of the laboratory manipulation (post-hoc test, $t = -0.53$, $df = 148.9$, adjusted $P = 0.595$). This suggests that corticosterone treated lizards decreased their energy storage and/or their food intake in the field resulting in a lower body mass relative to placebos. In addition, females from corticosterone treated group had much higher triglyceride levels than placebo group during the next reproductive season. Difference between sexes could be explained by the higher baseline corticosterone levels in females and its action on lipolysis (Peckett et al., 2011) and also by the additional costs associated with gestation. Indeed higher triglyceride levels in females suggest a higher energetic requirement to maintain reproduction output, and so a delayed cost of the past chronic enhancement of corticosterone.

4.3. Demographic and intergenerational effects

Contrary to our predictions, the chronic corticosterone elevation in the laboratory had no intra-generational delayed effects on demographic traits, including body size growth, annual survival, and future reproduction, and no inter-generational effects on the demographic traits of the first generation offspring. The absence of delayed, intra-generational effects is surprising because earlier studies using a grossly similar protocol (apart for feeding conditions) found higher annual survival rate of adult males following corticosterone enhancement (Cote et al., 2006). However, the present study included both adults and yearlings, and our sample size was too small to test for age- and sex-

dependent effect of corticosterone enhancement on survival with sufficient statistical power.

Inter-generational effects were predicted on the basis of earlier findings where reproductive traits of females and the phenotype of their offspring changed following a chronic increase in the baseline corticosterone concentration during gestation (Meylan and Clobert, 2005). In viviparous lizards, corticosterone elevation during gestation can impair embryonic development (Cree et al., 2003), decrease juvenile locomotor performance (Meylan and Clobert, 2004), inhibit juvenile growth rate (Meylan and Clobert, 2005) and promote juvenile philopatry (de Fraipont et al., 2000). In these previous studies, chronic elevation of the corticosterone was performed during gestation and maternal effects were tested in the same reproductive season. Instead, our experiment tested for delayed maternal effects in the next reproductive year of chronic exposure to corticosterone after gestation. In rats, it has been demonstrated that stress effects can persist in second-generation rats bred from females whose mothers were stressed during pregnancy (Pollard, 1986), with persistent effects into adulthood. For example, daughters of physically stressed mothers are less fertile and less fecund than daughters of unstressed mothers (Clark and Galef, 1995). The absence of inter-generational effects in our study might be explained by differences in term of timing of hormonal treatment. The corticosterone elevation took place outside gestation and 9 months before the next reproductive season, which might be too early to influence development and growth of the next generation of offspring.

Author contributions statement

S. M., J.-F. L.G. and R.J. designed the study. All authors contributed to protocols. R. J. analysed the data and wrote a first draft of the manuscript. S. M. and J.-F. L.G. contributed to writing.

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Data Accessibility

Data supporting the results in a paper will be archived in the public archive Dryad upon acceptance of the paper.

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