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Research paper

The repeatability of glucocorticoids: A review and meta-analysis

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ABSTRACT

Glucocorticoids are highly conserved hormones that mediate a suite of responses to changing conditions in vertebrates. Recent work has focused on understanding how selection operates on glucocorticoid secretion in natural populations. Because heritability is rarely estimated and difficult to measure in the wild, many studies report within-individual repeatability as an estimate of stable between individual differences in glucocorticoid secretion. We conducted a systematic review and meta-analysis on estimates of within-individual glucocorticoid repeatability to elucidate general patterns of repeatability, and to test for relationships between covariates and estimates of repeatability. To this end, we collected 203 estimates of within-individual glucocorticoid repeatability drawn from 71 separate studies and 55 species. Overall, we found moderate levels of repeatability (0.29). We also found that repeatability varied by sample type. Long-term measures (e.g., fecal and feather samples) and acute stress-induced plasma glucocorticoids had higher repeatability (long-term: 0.44, stress-induced: 0.38), than baseline glucocorticoid levels (0.18). Repeatability also decreased with increasing time between repeated sampling events. Despite significant overall repeatability, there was substantial heterogeneity in estimates from different studies, suggesting that repeatability of glucocorticoid secretion varies substantially across systems and conditions. We discuss the implications of our results for understanding selection on glucocorticoid traits and suggest that continuing work should focus on evaluating the repeatability of within-individual glucocorticoid reaction norms.

1. Introduction

Glucocorticoids are highly conserved vertebrate hormones that mediate a suite of functional responses to changing conditions over various time scales (Landys et al., 2006; Wingfield et al., 1998). Although responding appropriately to challenging conditions is critical in order to survive and reproduce, studying the evolution of glucocorticoid responses poses an empirical challenge (Bonier and Martin, 2016; Taff and Vitousek, 2016). While it is clear that selection should favor appropriate regulation of glucocorticoids, within-individual variation in secretion may mask any stable between-individual differences. Thus, it is often difficult to detect and interpret selection—or lack thereof—on variation in glucocorticoids (Bonier et al., 2009; Bonier and Martin, 2016). Indeed, glucocorticoids are so closely related to dynamic external conditions that many studies do not report analyses to detect stable between-individual differences in concentrations even when the same individuals are sampled repeatedly (e.g., many studies of primates listed in Table 1 of Cavigelli and Caruso, 2015). Despite the complications of measuring selection on highly flexible traits, a burgeoning body of literature has focused on understanding the way that selection operates on between-individual differences in glucocorticoid expression to produce appropriate phenotypic responses in changing conditions (Bonier et al., 2009; Bonier and Martin, 2016; Hau et al., 2016; Taff and Vitousek, 2016).

Glucocorticoid responses can clearly evolve in response to selection on secretion patterns (Pottinger et al., 1992). In the wild, many studies have looked for correlations between point estimates of glucocorticoid levels and survival or reproductive success; some of these studies demonstrate strong relationships, but patterns across studies are inconsistent (Bonier et al., 2009; Breuner et al., 2008; Sorenson et al., 2017). Further, it is often unclear from these studies whether between-individual differences in glucocorticoids are causal drivers of fitness outcomes, or whether external conditions alter both glucocorticoids and fitness directly (Bonier et al., 2009). Because most studies to date only follow one generation, they cannot estimate whether there is any evolutionary response to selection on glucocorticoid secretion. In captivity, strong selection regimes targeted at glucocorticoid secretion—or correlated traits—can generate lines that differ markedly in secretion patterns

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(e.g., Baugh et al., 2012; Evans et al., 2006; Pottinger and Carrick, 1999). However, it is unclear how similar these selection lines are to any selection regimes actually experienced in the wild. Only a few studies have directly measured heritability of glucocorticoid secretion under natural conditions (Jenkins et al., 2014; Stedman et al., 2017); these studies demonstrate low to moderate heritability of glucocorticoid traits.

Given the paucity of field-based estimates of heritability, many recent studies report the repeatability of glucocorticoid traits within individuals in order to demonstrate the existence of stable between-individual differences (e.g., Cockrem et al., 2016; Ouyang et al., 2011). When individuals are sampled at least twice, repeatability can be estimated as the intra-class correlation coefficient (ICC) by calculating the proportion of total variance in a trait that occurs between- rather than within-individuals (Lessells and Boag, 1987; Nakagawa and Schielzeth, 2010). Repeatability is sometimes reported using different methods (correlations, ANOVA, or linear mixed models [LMMs]) and can be reported as 'agreement repeatability'—the similarity of absolute values between repeated measures—or as 'adjusted repeatability'—the similarity between repeated measures after accounting for covariates (recent papers demonstrate that LMM's typically perform better and have several advantages over other estimation approaches; Baugh et al., 2014; Nakagawa and Schielzeth, 2010). Regardless of the methods used, repeatability measures are sometimes presented—implicitly or explicitly—as an upper bound estimate of heritability (sensu, Boake, 1989). Although this assertion holds under certain conditions, there are good reasons to believe that glucocorticoid measures will often violate these assumptions (Dohm, 2002). Still, repeatability provides a tractable, if imperfect, indication of stable between-individual differences in glucocorticoid secretion patterns. While some studies report high repeatabilities for glucocorticoid traits (e.g., Angelier et al., 2010; Narayan et al., 2013; Rogovin and Naidenko, 2011), others fail to detect any repeatability (e.g., Bridge et al., 2009; Pavitt et al., 2016; Tempel and Gutierrez, 2004). In some cases, low repeatability may not reflect a lack of between-individual differences, but rather the effect of heterogeneous external conditions, such as uncontrolled variation in food availability or temperature. Conversely, some reports of high repeatability may reflect persistent environmental differences between individuals, rather than stable phenotypic differences *per se* (i.e., pseudo-repeatability; Niemelä and Dingemanse, 2017). To date, no comprehensive review of the repeatability of glucocorticoid traits has been published, and it is difficult to interpret the generality of available estimates of glucocorticoid repeatability.

Here, we provide a systematic review and meta-analysis on estimates of glucocorticoid repeatability in vertebrates. Several recent papers have included discussions of glucocorticoid repeatability, but these qualitative reviews do not compile a comprehensive set of repeatability estimates or conduct any analyses to uncover general patterns about glucocorticoid repeatability (Cockrem, 2013; Cockrem et al., 2009; Hau et al., 2016; Ouyang et al., 2011). Holtmann et al. (2017) recently included estimates of corticosterone repeatability in a meta-analytical framework, but their analysis included only birds, grouped several hormone types (i.e., glucocorticoids, estrogens, and androgens) and sample substrates together, and was not focused on evaluating the repeatability of glucocorticoid secretion *per se*. In our analysis, we expand on the studies identified by Holtmann et al. (2017) to provide a broad overview of how repeatable glucocorticoid concentrations are in vertebrates. We also use this dataset to assess whether estimates of repeatability are correlated with relevant covariates, including taxon, sample size, baseline versus stress-induced measures, captive versus wild studies, and the sampling interval. Finally, we discuss the limitations of using repeatability as a proxy for evolvability in highly labile traits, and make some suggestions for future studies in this area.

2. Methods

2.1. Literature search

We conducted a meta-analysis on estimates of within-individual glucocorticoid repeatability in vertebrates. We searched for studies to include in our analysis using a combination of approaches. Initially, we consulted a recently published meta-analysis of hormonal, metabolic, and behavioral repeatability in birds (Holtmann et al., 2017); this study included estimates of corticosterone repeatability in birds from a literature search that was conducted in February 2015. We manually checked each entry from that database to confirm suitability for our purposes and extracted additional covariates to be used in our analyses (see below). For some studies included in Holtmann et al. (2017), repeatability estimates were not included in the originally published reports but communicated directly to the authors; we included these effect sizes in our dataset (using the values provided by Holtmann et al. (2017)), but did not confirm repeatability independently.

We added additional studies by conducting a literature search to find studies on birds that were published from 2015 to 2016 as well as studies on other vertebrate taxa published at any time. In addition to this broad search, we conducted both a backwards- and forwards-search of articles that were cited by—or cited—key papers that include discussions of glucocorticoid repeatability (e.g., Cockrem, 2013; Cockrem et al., 2009; Dantzer et al., 2010; Fletcher et al., 2015; Hau et al., 2016; Ouyang et al., 2011). For each of these approaches, we updated our searches to include papers that were published on or before December 31st, 2016.

2.2. Inclusion criteria

To be included in our analyses, studies had to meet six main criteria. First, we only included studies that reported repeatability as an intra-class correlation coefficient (ICC) using an ANOVA based (Lessells and Boag, 1987) or Linear Mixed Model (LMM) Based approach (Nakagawa and Schielzeth, 2010), a Spearman correlation, or a Pearson correlation (r). We were able to include a few studies where repeatability was not reported explicitly by calculating repeatability with data extracted from a scatterplot using WebPlotDigitizer version 3.9 (Ankit Rohatgi, Austin, Texas, USA). In these cases, we calculated repeatability using LMMs and the *rptR* package in R (Stoffel et al., 2017). The LMM approach is constrained to yield positive values; for low repeatabilities (<0.005), we followed Holtmann et al. (2017) in recalculating repeatabilities using an ANOVA based approach because these estimates better fit the normality assumptions of our meta-analytic models. Second, we excluded studies that were conducted on domesticated animals, humans, inbred lines of lab animals, or artificially selected strains (particularly strains selected for high or low glucocorticoid responsiveness). Third, we excluded studies that conducted experimental manipulations that could have influenced glucocorticoid expression, except in cases where a control group was reported separately. Fourth, we excluded studies that calculated repeatability based on samples that did not distinguish between baseline and stress-induced glucocorticoid levels. Fifth, we included studies that were conducted on adult animals only. Finally, we excluded studies that did not provide enough supporting details to be included in our analyses (e.g., number of measurements per individual, season that samples were collected, etc.).

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