doi:10.1111/evo.12795

Environmental effects on the structure of the G-matrix

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Received May 14, 2015
Accepted September 22, 2015

Genetic correlations between traits determine the multivariate response to selection in the short term, and thereby play a causal role in evolutionary change. Although individual studies have documented environmentally induced changes in genetic correlations, the nature and extent of environmental effects on multivariate genetic architecture across species and environments remain largely uncharacterized. We reviewed the literature for estimates of the genetic variance–covariance (G) matrix in multiple environments, and compared differences in G between environments to the divergence in G between conspecific populations (measured in a common garden). We found that the predicted evolutionary trajectory differed as strongly between environments as it did between populations. Between-environment differences in the underlying structure of G (total genetic variance and the relative magnitude and orientation of genetic correlations) were equal to or greater than between-population differences. Neither environmental novelty, nor the difference in mean phenotype predicted these differences in G. Our results suggest that environmental effects on multivariate genetic architecture may be comparable to the divergence that accumulates over dozens or hundreds of generations between populations. We outline avenues of future research to address the limitations of existing data and characterize the extent to which lability in genetic correlations shapes evolution in changing environments.

KEY WORDS: **Cryptic genetic variation, G-matrix constancy, genetic architecture, matrix comparison, response to selection.**

The genetic variance–covariance matrix (**G**) describes the magnitude and orientation of the axes of quantitative genetic variation in a population, which affect the rate and direction of the response to selection (Lande 1979; Schluter 1996; Chenoweth et al. 2010). **G** is not static. Changes in genetic covariances have been documented over both short and long timescales (reviewed in Roff and Mousseau 1999; Arnold et al. 2008). Given that **G** evolves, the crucial question is now how quickly and under what circumstances it does so (Steppan et al. 2002; Doroszuk et al. 2008). If **G** is conserved over long timescales, existing genetic covariances accurately reflect historical and future genetic constraints on the multivariate evolutionary response. However, if rapid change in **G** is common, evolutionary trajectories may be unpredictable on timescales as short as a few generations (Phillips and McGuigan 2006).

The environment is an underappreciated but potentially pervasive source of rapid change in **G**. Environmental effects on **G** challenge the prevailing assumption that multivariate genetic architecture is stable over short periods of time (Sgrò and Hoffman 2004). The potential for rapid change in **G** depends on the processes that shape allele frequencies and allelic effects, the building blocks of genetic variances and covariances (Falconer and Mackay 1996). To date, most research on the constancy of **G** has focused on allele frequency changes driven by selection, migration, mutation, and genetic drift (Roff 2000; McGuigan 2006; Phillips and McGuigan 2006; Arnold et al. 2008). However, environment-specific allelic effects have the potential to alter genetic covariances in a single generation much more rapidly than allele frequency changes typically accumulate. Environment-specific allelic effects occur when the average effect of an allele on phenotype depends on the environment in which it is expressed (de Jong 1990), often as a result of among-family differences in environment-specific gene expression. For example, the effect of the *Eda* locus on growth rate in stickleback depends on the salinity of the developmental environment (Barrett et al. 2009), and herbivory resistance

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is governed by different QTL in spring- and fall-germinating *Arabidopsis* (Weinig et al. 2003). Environment-specific allelic effects are likely to alter genetic covariances whenever two covarying traits exhibit differential environmental sensitivity.

If the environment strongly impacts multivariate genetic architecture (i.e., if environment-specific allelic effects are common), environmental change may release prior genetic constraints or introduce new ones in a single generation, shaping the rate and direction of adaptive evolution even in the absence of variation in selection among environments (McGuigan and Sgrò 2009). Even under identical selection regimes, environmental effects on genetic architecture may contribute to the maintenance of genetic variation by altering the genetic basis of phenotypic variation, and therefore, the genomic regions that are subject to selection (McGuigan and Sgrò 2009; Paaby and Rockman 2014). Finally, adaptation to changing climates, anthropogenic disturbance, and novel ecological niches may be less predictable than is currently appreciated if existing genetic architecture does not persist in new environments.

A growing body of empirical studies demonstrates that the environment can change genetic variances and covariances (Sgrò and Hoffman 2004; Pigliucci 2005; Doroszuk et al. 2008; Eroukhmanoff and Svensson 2011; Johansson et al. 2012; Sikkink et al. 2015). However, it remains unclear whether environmental effects on **G** are common enough to challenge the assumption that **G** is predominately stable in the short term (Scheiner 1993). The evolutionary consequences of environmental effects on **G** depend on two unresolved questions. First, how strong are environmental effects on multivariate genetic architecture relative to selection, mutation, migration, and drift? If differences in genetic architecture between environments are negligible relative to the differences that accumulate between diverging populations, short-term changes in genetic architecture may not exert strong influence on the evolutionary response. On the other hand, if the environment induces change in **G** that is comparable to the divergence observed over dozens or hundreds of generations, **G** may vary substantially in heterogeneous environments over short timescales.

Second, what environmental differences precipitate the largest changes in **G**? The evolutionary consequences of change in **G** depend on the environmental conditions that trigger change (Charmantier and Garant 2005; Paaby and Rockman 2014). Answering this question requires a metric of differences between environments that can be applied regardless of the manipulation employed in any given study. One potential approach is to identify the types of environmental conditions that restructure **G**. A promising candidate is environmental novelty. Novel environments are thought to perturb the genotype-to-phenotype map and reshape genetic architecture, although empirical evidence linking novelty to the release of genetic variation remains equivocal (McGuigan and Sgrò 2009; Ledón-Rettig et al. 2014). An alternative to this environment-centric approach is a phenotype-centric one: using the phenotype as a barometer of environmental difference to determine whether the environments that change phenotype means drive corresponding change in **G**.

To assess the evolutionary implications of environmentally induced change in **G**, we surveyed the literature for studies that measured **G** in different environments. We compared differences in **G** between environments to differences in **G** between conspecific populations (when the latter are compared in a common environment) to determine how strong environmental effects on **G** are relative to the combined action of selection, mutation, migration, and drift. We asked three questions: How large are between-environment differences in the predicted evolutionary trajectory relative to differences between populations? How large are between-environment differences in the structure of **G** relative to differences between populations? Finally, what types of environmental difference precipitate the largest changes in **G**?

Methods

DATASET

We searched the literature for studies that reported broad- or narrow-sense genetic covariances or correlations (variance-scaled covariances) between at least two traits. We performed our search in Web of Science and Dryad using the search terms "G matrix," "genetic correlation," "genetic covariance," "comparison," and "environment," and supplemented the results of this search with studies cited in the papers identified. Several of the studies in our dataset came from two previous reviews (Sgrò and Hoffman 2004 and Pitchers et al. 2014). Two studies estimated **G** separately for males and females; in these cases we arbitrarily selected only one sex for our analysis. When **G** was estimated in more than two environments, we compared the two most quantitatively different environments (Charmantier and Garant 2005).

For our between-environment G-matrix comparisons, we only included experimental studies that reared the same source population under different environmental conditions. These studies either varied one or two environmental variables (e.g., temperature, nutrient availability, etc.) under controlled conditions, or transplanted a single source population into different natural environments (e.g., different parts of the species' range). This dataset thus reflects, as closely as possible, differences in **G** due only to environment-specific allelic effects. For our between-population G-matrix comparisons, we only included studies that reared different conspecific source populations under common garden conditions. This dataset predominately reflects differences in **G** due to allele frequency differences in the source populations, although evolved differences in allelic effects (e.g., genotype-by-environment interactions in the common garden

environment) may also contribute to differences in **G** between populations.

The studies in our dataset used a variety of methods to compare G-matrices, so we could not directly incorporate the results of their analyses into our meta-analysis. Instead, we conducted our own set of matrix comparison tests on the G-matrices that they reported, treating each matrix as a point estimate. To account for the fact that this approach ignores error in estimating **G** (which is substantial; Cheverud 1988), we included the sample size used to build each original G-matrix as a covariate in our analyses. We used sample size as a covariate, rather than as a weight, because we expected that studies with smaller sample size would exhibit larger differences in **G** due to sampling error; including sample size as a covariate statistically controls for a linear relationship between sample size and the difference in **G** when assessing significance of other effects in the model. The sample size for narrow-sense G-matrices is the number of half-sib families; for broad-sense G-matrices, it is the number of full-sib families or genotypes (when clones or recombinant inbred lines were used). Three studies in our dataset estimated **G** using animal models. Because sample sizes in animal model analyses are generally reported as the number of individuals rather than the number of families, we excluded these G-matrices from any analyses that included sample size.

In our analyses, we also included the number of traits in **G** and the interaction between number of traits and comparison type (between populations and environments). We did so because we suspected that studies that compared multivariate genetic architecture in only a few traits had stronger a priori reasons for choosing those traits than studies that included many traits. We expected this to have a stronger impact on the environment dataset because many studies that measured environmental effects on genetic correlations in a small number of traits selected traits for which they hypothesized a trade-off.

A third of the G-matrices in our dataset (66 of 200 matrices; Table S1) contained negative eigenvalues, which is not uncommon when matrices are built using variance component estimation (Hill and Thompson 1978). For each matrix, we calculated the proportion of variance contained in negative eigenvalues as the absolute value of the sum of negative eigenvalues divided by the sum of the absolute values of all eigenvalues. We excluded five comparisons for which one or both matrices contained greater than or equal to 20% of the variance in negative eigenvalues, leaving a total of 95 comparisons. We "bent" the remaining matrices containing negative eigenvalues by replacing all negative eigenvalues with small positive numbers (1.0×10^{-6}) because many matrix comparison tests require positive definite matrices (Hayes and Hill 1981; Phillips and Arnold 1999; Chapuis et al. 2008). Matrix bending is a potential source of bias (Phillips and Arnold 1989), but the bias that it introduced in our dataset was likely small, because the negative eigenvalues accounted for a small percentage of the total variance in the remaining nonpositive definite matrices (mean: 4.1%, median: 2.5%, range: 0.00000001–16.7%).

Genetic covariance matrices were only available for approximately half of the studies in our dataset (43 of 95; the remainder reported correlation matrices), so we converted covariance matrices to correlation matrices for all comparisons except total genetic variance (see below). We omitted any traits with an estimated genetic variance of zero. All analyses were performed in R version 3.1.0 (R Core Team 2014) using sum-to-zero contrasts for unordered factors ("contr. sum" in R). For all analyses described below, we determined that the data did not violate the distributional assumptions of general linear models (normality of residual variation and homogeneity of variance) based on visual assessment of plots of the residuals against fitted values and normal quantile–quantile plots.

COMPARISONS OF THE PREDICTED EVOLUTIONARY TRAJECTORY

We compared the predicted evolutionary trajectories caused by each pair of G-matrices (from two environments or two populations) to evaluate the evolutionary consequences of differences in **G**. We used random skewers to measure the difference in the predicted evolutionary trajectory for each pair of G-matrices (Cheverud 1996). Random skewers applies random selection gradients to two matrices and measures the difference in their responses to selection in multivariate trait space. We applied 1000 random selection gradients drawn from a uniform distribution on the interval (−1,1) to each G-matrix, and calculated the multivariate response to selection for each gradient using the multivariate breeder's equation, resulting in 1000 response vectors per G-matrix. We used a modified version of the R function RAND.SKEWER provided in Roff et al. (2012) for this analysis.

We compared the predicted evolutionary trajectory for each pair of G-matrices by calculating the overall response difference for each pair (Fig. 1A). The response difference measures the distance between the endpoints of the two response vectors when a random linear selection gradient is applied to two G-matrices. This metric describes the magnitude of evolutionary divergence caused by differences in the structure of **G**, and is calculated as:

$$d\ (\boldsymbol{\beta}) = \sqrt{\boldsymbol{\beta}'(\boldsymbol{G}_1 - \boldsymbol{G}_2)^2\boldsymbol{\beta}},$$

where $\boldsymbol{\beta}$ is a randomly drawn linear selection gradient (eq. 7 in Hansen and Houle 2008). We used the mean response difference across 1000 randomly generated linear selection gradients as our metric of the overall response difference. To test whether the difference in the evolutionary response between populations was significantly different from the difference between environments, we ran a general linear model using the lm function in R with the

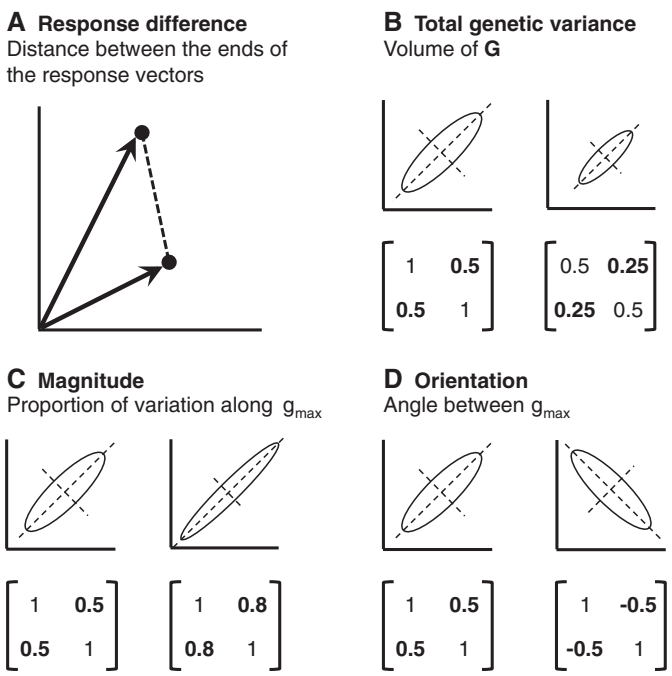

Figure 1. The metrics used to compare G. (A) Metric of the difference in the predicted evolutionary trajectory between two G-matrices. The graph shows the multivariate response to selection for two hypothetical traits (one hypothetical trait is on the *x*-axis and one is on the *y*-axis). The two vectors indicate the direction of the response to selection in the two G-matrices. (B–D) Metrics of difference in the structure of two G-matrices. The two graphs in each panel show the correlation between two hypothetical traits (one on the *x*-axis and one on the *y*-axis), with the corresponding G-matrix depicted in the bottom row.

response difference as the dependent variable. The independent variables in this regression were comparison type (between environments or between populations), the number of traits in **G** and their interaction, and the sample size used to build **G**. We tested significance using the analysis of variance (ANOVA) function and type III sums of squares in the *car* package (Fox and Weisberg 2011).

We performed a similar analysis to measure the difference in the direction of the response between two matrices. We calculated the angle between their response vectors for each of the 1000 pairs of response vectors as (Ingleby et al. 2014; Teplitsky et al. 2014):

$$\theta = \frac{180}{\pi} \times \cos^{-1}\left(\frac{\boldsymbol{\Delta}\bar{\boldsymbol{z}}_1 \cdot \boldsymbol{\Delta}\bar{\boldsymbol{z}}_2}{\sqrt{\boldsymbol{\Delta}\bar{\boldsymbol{z}}_1 \cdot \boldsymbol{\Delta}\bar{\boldsymbol{z}}_1}\sqrt{\boldsymbol{\Delta}\bar{\boldsymbol{z}}_2 \cdot \boldsymbol{\Delta}\bar{\boldsymbol{z}}_2}}\right).$$

We used the mean angle between the responses for each matrix pair as our metric of the difference in the direction of the response. This analysis produced qualitatively similar results to the analysis of the overall response difference, so we only present the results for the response difference in text; the results for the direction of the response are reported in Table S2 and Figure S1.

COMPARISONS OF G-MATRIX STRUCTURE

For each pair of G-matrices sampled from two environments or two populations, we calculated the difference in three metrics of matrix structure: total genetic variance, the relative magnitude of genetic correlations, and orientation of genetic correlations (Phillips and Arnold 1999; Fig. 1B to D). To test whether differences in the structure of **G** between environments were significantly smaller or larger than differences in the structure of **G** between populations, we ran a separate general linear model for each matrix comparison metric described below using the lm function in R. The independent variables in these regressions were comparison type (between environments or between populations), the number of traits in **G**, and their interaction, and the sample size used to build **G**. We tested significance using the ANOVA function and type III sums of squares in the *car* package (Fox and Weisberg 2011).

Total genetic variance reflects the genetic variation available to selection in the multivariate phenotype (across all traits); differences in total genetic variance result in differences in the rate of the evolutionary response (Fig. 1B). We refer to this metric as "total genetic variance" rather than "total additive genetic variance" because our dataset contained both narrow- and broad-sense G-matrices, and the latter include both additive and non-additive components of variation. To measure the difference in total genetic variance for a pair of G-matrices, we calculated the total genetic variance of each matrix, v_T, as $\sum_{i=1}^{n} \lambda_i$, where λ are its eigenvalues (Kirkpatrick 2009). For each comparison, we then calculated the difference in total genetic variance between the two matrices as:

$$\frac{|v_{T1} - v_{T2}|}{\left(\frac{v_{T1}+v_{T2}}{2}\right)},$$

which standardizes the difference by the mean total genetic variance. This analysis was only performed for the 43 comparisons for which covariance matrices were available because the total genetic variance of a correlation matrix is constrained to equal the number of traits.

The relative magnitude of genetic correlations describes the proportion of genetic variation that falls along the major axis (Fig. 1C). A difference in relative magnitude results in differences in the degree of genetic constraint in the most accessible evolutionary direction (Roff et al. 2012). To measure the difference in the magnitude of genetic correlations for a pair of G-matrices, we calculated the difference in the proportion of variance along the major axis of variation (hereafter, "$\mathbf{g}_{max}$") for each comparison. The proportion of variance along $\mathbf{g}_{max}$ measures the fraction of total genetic variation that is found along the first eigenvector, and is given by:

$$\lambda_1 \Big/ \sum_{i=1}^{n} \lambda_i,$$

where λ_i are the eigenvalues ordered from largest to smallest (Kirkpatrick 2009). For each matrix pair, we calculated the absolute value of the difference between these fractions.

The orientation of genetic correlations describes which dimensions of the multivariate phenotype are most strongly correlated (Roff et al. 2012; Fig. 1D). Differences in the orientation of **G** reflect fundamental disparities in genetic constraint and in the most accessible direction of evolution. To measure the difference in the orientation of genetic correlations for a pair of G-matrices, we calculated the angle between their major axes of variation (i.e., $\mathbf{g}_{\max}$). The angle between the $\mathbf{g}_{\max}$ vectors was calculated as (Ingleby et al. 2014; Teplitsky et al. 2014):

$$\theta = \frac{180}{\pi} \times \cos^{-1}\left(\frac{\boldsymbol{g}_{\max_1} \cdot \boldsymbol{g}_{\max_2}}{\sqrt{\boldsymbol{g}_{\max_1} \cdot \boldsymbol{g}_{\max_1}}\sqrt{\boldsymbol{g}_{\max_2} \cdot \boldsymbol{g}_{\max_2}}}\right).$$

This calculation results in values ranging from 0° to 180°, so we subtracted from 180° any angles in the range $90° \leq x \leq 180°$ so all angles were between 0° and 90°. An angle of 0° indicates no difference in orientation, and an angle of 90° indicates that the major axes of genetic variation in the two environments or populations are orthogonal. For correlation matrices containing only two traits, this value is constrained to equal 0° or 90° (see Fig. 2D).

Differences in the orientation of **G** can result from a change in the direction of the major axis of variation or from reordering of the eigenvectors such that the major axis of variation in one G-matrix corresponds to one of the minor axes of variation in the other. To account for this possibility, we used Krzanowski's similarity index to compare the orientation of the subspaces of the original matrices that account for the most genetic variation using a subset (half or fewer) of their principal components (Krzanowski 1979; Blows et al. 2004; Aguirre et al. 2014). A similarity index of 1 means that the orientation of the two subspaces in multivariate trait space is identical, and a value of 0 means that the two subspaces are orthogonal. We conducted this analysis using a modified version of the krzanowski.test function in the *MCMCglmm* package in R (Hadfield 2010). This analysis produced results that were qualitatively similar to the analysis using the angle between $\mathbf{g}_{\max}$ (Table S2 and Fig. S1), suggesting that differences in the orientation of **G** in our dataset are primarily due to changes in the direction of $\mathbf{g}_{\max}$ rather than reordering of the eigenvectors.

WHAT ENVIRONMENTAL CONDITIONS CHANGE G?

A crucial step in evaluating the evolutionary consequences of environmental effects on **G** is identifying the environmental conditions that change **G**. We examined two metrics of environmental difference that were available for most of the studies in our environment dataset: environmental novelty and the environmental effect on phenotype.

Novel environments are thought to alter genetic architecture because they perturb evolved phenotypic buffering mechanisms (Paaby and Rockman 2014). We tested whether there was a larger difference in **G** in comparisons between novel and nonnovel environments than in comparisons between two nonnovel environments. We only included comparisons for which the original study categorized both environments as novel or nonnovel ($N = 43$) based on the original authors' assessment of whether the environmental treatment was outside the typical range of conditions the organism experiences. We ran a separate model for each matrix comparison metric using the lm function, with each metric as the dependent variable and environmental novelty as the independent variable, and tested significance using the ANOVA function and type III sums of squares in the *car* package (Fox and Weisberg 2011). We included number of traits in **G** and sample size as covariates in this analysis.

For our second metric of environmental difference we used the difference between environments in phenotype means, assuming that very different environmental conditions are more likely to produce large differences in phenotypic expression. To measure the between-environment difference in phenotype means for each comparison, we calculated the difference in the phenotype mean between the two environments, standardized by dividing by their pooled standard deviation, and took the absolute value (eq. 1 in Nakagawa and Cuthill 2007). We repeated this for all measured phenotypes, and used the median of this standardized difference across all phenotypes reported in each study as our measure of between-environment difference in mean phenotype. We calculated this index for all studies in which the phenotype means were available in text, in supplementary materials, estimable from figures, or obtainable from Dryad ($N = 34$).

We tested whether the difference in phenotype means between environments predicted the environmental effect on **G** by regressing each matrix comparison metric on this index. We included the number of traits in each G-matrix and the sample size in our analysis as covariates, and tested significance using the ANOVA function and type III sums of squares in the *car* package (Fox and Weisberg 2011). We repeated this analysis for two other measures of between-environment difference in mean phenotype for each comparison: the maximum of the standardized phenotype difference across all phenotypes, hypothesizing that the most environmentally responsive trait may be the best predictor of difference in **G**; and the variance in the standardized phenotype difference across all phenotypes, hypothesizing that variation in environmental sensitivity among traits may underlie differences in **G**. Both analyses produced qualitatively similar

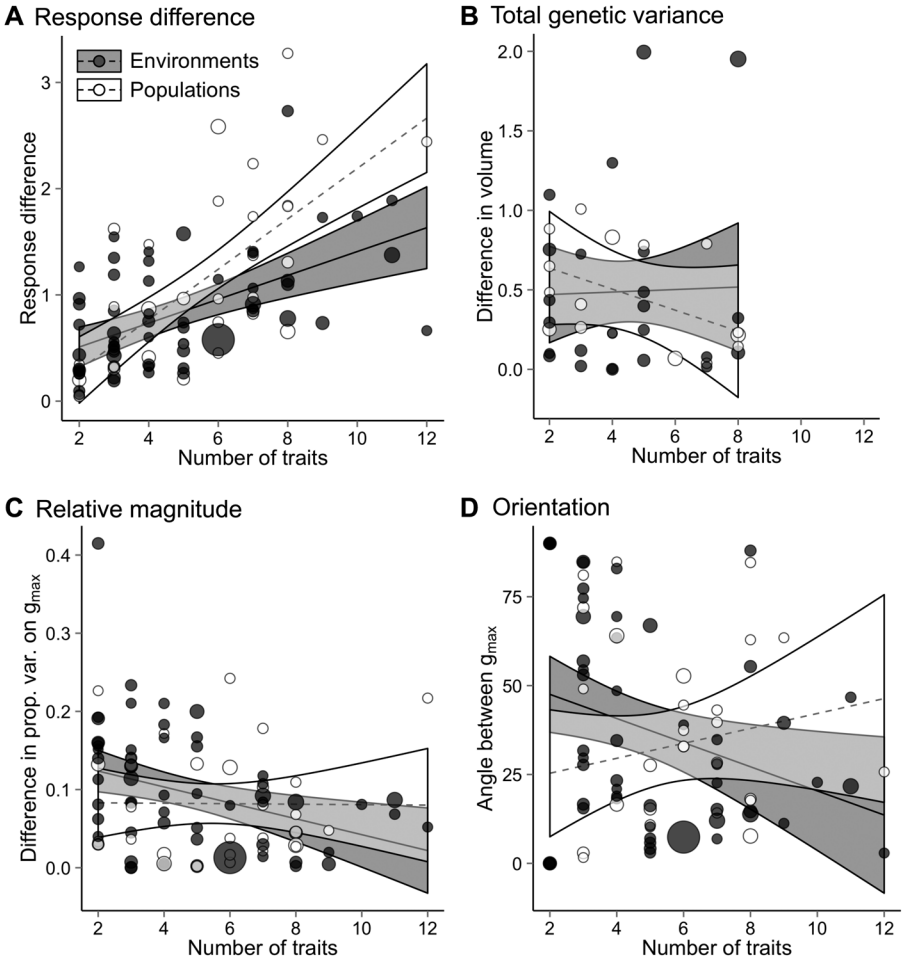

Figure 2. Differences in the predicted evolutionary trajectory (A) and the structure of G (B–D) in between-environment (gray) and between-population (white) comparisons. Each datapoint is a single comparison of two G-matrices, scaled by the sample size used to estimate G. The *x*-axis is the number of traits in G. See Table 1 for statistics. The results are not qualitatively affected by the removal of the outlier in the upper left corner in panel (C).

results to the median-based analysis, so we do not report the results here.

Results

We identified 95 G-matrix comparisons (pairs of G-matrices) from 81 studies published between 1981 and 2014 that reported genetic covariance or correlation matrices for 2–12 traits (Appendix S1, Table S1). Sixty-one of these comparisons were between environments and 34 were comparisons between conspecific populations. The data were heavily taxonomically biased: 75 comparisons were from plant or insect systems, and only three genera (*Drosophila*, *Arabidopsis*, and *Gryllus*) accounted for nearly a quarter of all comparisons. This distribution almost certainly reflects the state of the field, rather than systematic bias in our literature search, because the measurement of **G** is a time-consuming and data-hungry endeavor that is most feasible in species with short generation times that can be raised in the laboratory. The environmental manipulation varied broadly among the studies that compared G in different environments. Most studies involved laboratory-based manipulations of diet, temperature, water, light availability, and photoperiod (41 of 61; Table S1).

The composition of the between-population and between-environment datasets differed in several respects. The between-population dataset was more taxonomically diverse than the between-environment dataset (Table S1), in that it included a few major taxonomic groups missing from the between-environment dataset (fish, crustaceans, and reptiles), and was less dominated by plants and insects (62% of between-population comparisons vs. 89% of between-environment comparisons). There were methodological differences between the two groups as well. The mean sample size was slightly, but not significantly, higher in the between-environment dataset (between environments: 57.9, between populations: 41.7; $F_{1,89} = 0.775$, $P = 0.381$). The mean

number of traits in **G** was slightly, but not significantly, higher in the between-population dataset (between environments: 4.7, between populations: 5.4; $F_{1,89} = 1.918$, $P = 0.170$). As a result, the ratio of the sample size to the number of traits in **G** was higher in the between-population dataset than the between-environment dataset (14.5 samples per trait vs. 9.8, respectively). Because we included both sample size and number of traits in **G** as covariates in our analyses, these differences are unlikely to have contributed to our results.

Our dataset included both narrow- and broad-sense estimates of **G** ($N = 38$ and 57 comparisons, respectively). The proportional representation of these two types of G-matrices was similar in the between-environment and between-population datasets (narrow-sense: 38 and 44%, respectively; $\chi^2 = 0.155$, df $= 1$, $P = 0.694$). There was no significant difference between narrow- and broad-sense estimates in the difference in **G** for any matrix comparison metric (Table S4), indicating that this methodological difference among studies does not contribute to our results.

COMPARISONS OF THE PREDICTED EVOLUTIONARY TRAJECTORY

The response difference of the between-environment and between-population comparisons did not differ significantly (Fig. 2A, Table 1). However, there was a significant comparison × number of traits interaction, suggesting that the effect of comparison type depends on the number of traits in **G** (Table 1). Although the response difference for G-matrices with few traits was similar in the between-environment and between-population comparisons, the response difference for G-matrices with many traits differed more between populations than between environments (Fig. 2A).

The differences in G-matrix structure documented above did not result in major differences in the predicted evolutionary response for most matrix pairs (median angle between the response vectors: 23.3°). The results were qualitatively similar for the direction of the response and the response difference (Tables 1 and S2; Figs. 2A and S1A), which indicates that the majority of the overall difference in the evolutionary response is due to a change in the angle, rather than the magnitude, of the response vector.

COMPARISONS OF G-MATRIX STRUCTURE

The three metrics of difference in G-matrix structure were only weakly correlated with one another (Table 2), indicating that change in one aspect of **G** does not necessarily translate to strong effects on another. The difference in the orientation of **G** was significantly correlated with the response difference (Table 2), an unsurprising result given that these metrics reflect major differences in genetic architecture.

The magnitude of differences in total genetic variance in both the between-environment and between-population comparisons was highly variable, ranging from 0% to nearly 200% (Fig. 2B). Differences in the relative magnitude of genetic correlations were small (Fig. 2C). However, differences in the orientation of genetic correlations were moderate to large, especially between environments; in many comparisons, the major axes of genetic variation between the two G-matrices were nearly orthogonal (angles near 90°; Fig. 2D). The largest differences occurred between matrices that included a small number of traits, a pattern that was especially pronounced for between-environment comparisons. This result may reflect investigation bias: studies that examined only a few traits may have selected those traits because they were hypothesized to be environmentally responsive.

Differences in the structure of **G** between environments were equal to or greater than differences in **G** between conspecific populations. For two of the three metrics of G-matrix structure—total genetic variation and the relative magnitude of genetic correlations—divergence in **G** between environments was not significantly different from divergence in **G** between conspecific populations (Fig. 2B and C, Table 1). The orientation of genetic correlations differed more between environments than between populations, although there was a significant comparison × number of traits interaction, suggesting that the effect of comparison type depends on the number of traits in **G** (Fig. 2D, Table 1).

WHAT ENVIRONMENTAL CONDITIONS CHANGE G?

Differences in the structure of **G** and the predicted evolutionary response were not significantly larger in comparisons involving novel environments (Fig. 3, Table 3). Similarly, the environmental effect on mean phenotype was a poor predictor of the effect of the environment on **G** (Fig. 4, Table 3). There was no relationship between the environmental effect on mean phenotype and the difference in total genetic variance, relative magnitude of genetic correlations, the orientation of genetic correlations, or the response difference.

Discussion

Our results suggest that the environment is capable of generating large differences in multivariate genetic architecture that are comparable in magnitude to the differences between conspecific populations. These data indicate that environmental shifts can induce changes in genetic architecture within a single generation comparable to those that accumulate in many generations as populations diverge due to the combined action of selection, mutation, migration, and drift. Neither environmental novelty nor differences in phenotype means predicted between-environment differences in the structure of **G** or the predicted evolutionary trajectory, emphasizing the need to develop a predictive framework for the ecological conditions that precipitate changes in

Table 1. Results from general linear models testing for differences in G between environments and between populations ("Comparison" in the table).

	Evolutionary trajectory		Structure of **G**					
	Response difference		Total genetic variance		Relative magnitude		Orientation	
	$F_{1,87}$	P	$F_{1,35}$	P	$F_{1,87}$	P	$F_{1,87}$	P
Comparison	3.126	0.081	0.769	0.386	2.612	0.110	**4.857**	**0.030**
N. traits	**59.813**	**<0.001**	0.640	0.429	2.668	0.106	0.251	0.618
Sample size	1.936	0.168	3.944	0.055	1.210	0.274	0.688	0.409
Comparison × n. traits	**7.551**	**0.007**	1.061	0.310	2.353	0.129	**4.484**	**0.037**

A separate model was run with each of the four matrix comparison metrics as the dependent variable. "N. traits" = number of traits in G; "sample size" = number of half-sib families (narrow-sense G-matrices) or full-sib families or genotypes (broad-sense G-matrices) used to estimate G. Bold entries are significant ($\alpha = 0.05$).

Table 2. Spearman's correlations between changes in different aspects of G.

	Evolutionary trajectory	Structure of **G**		
	Response difference	Total genetic variance	Relative magnitude	Orientation
Response difference	*95*	−0.15 (1.000)	0.16 (0.645)	**0.44 (<0.001)**
Total genetic variance		*43*	0.24 (0.645)	−0.07 (1.000)
Relative magnitude			*95*	0.08 (1.000)
Orientation				*95*

***P* values after sequential Holm–Bonferroni correction are in parentheses, and significant correlations are indicated in bold. Sample sizes for each correlation are along the diagonal.**

genetic architecture. Our results indicate that the environment can shape multivariate genetic architecture directly, and deserves attention as an important factor that governs the structure of genetic constraint (Jones et al. 2003; Eroukhmanoff and Svensson 2011; Björklund et al. 2013; Sikkink et al. 2015). Moreover, our meta-analysis stresses the need for future research that addresses limitations of the existing data. We argue that the nature of environmental effects on genetic architecture therefore remains an empirical problem (Walsh and Lynch 2015), and we conclude by highlighting productive avenues of future research.

WHAT ARE THE EVOLUTIONARY CONSEQUENCES OF ENVIRONMENTAL EFFECTS ON G?

The predicted evolutionary trajectory differed as strongly between environments as it did between conspecific populations (Fig. 2A, Table 1). However, while the response difference between environments and populations was similar for small matrices, there was a significant comparison-by-number of traits interaction indicative of larger differences in the evolutionary response in between-population comparisons of matrices with many traits. This statistical interaction may indicate that differences in the evolutionary trajectory between environments are largely due to a small number of traits that are strongly environmentally sensitive, whereas differences between populations result from accumulated differences in the genetic architecture of the entire multivariate phenotype, although our data do not address this hypothesis explicitly. Alternatively, this interaction may be a signature of differential sampling bias in the environment and population datasets. Studies that compared genetic correlations in different environments—especially those that measured only a few traits—may have focused on traits hypothesized to be environmentally responsive, whereas studies comparing populations may have sampled traits more broadly across the multivariate phenotype.

Ultimately, the long-term evolutionary consequences of the differences in **G** between environments and populations may be minor if they are relatively ephemeral, average out over longer timescales, or decay in the face of strong selection (Delph et al. 2011; Walsh and Lynch 2015). Even transient change in multivariate genetic architecture can have a lasting impact on the evolutionary trajectory if the change in **G** shifts the population to a flatter or steeper region of the adaptive landscape, altering

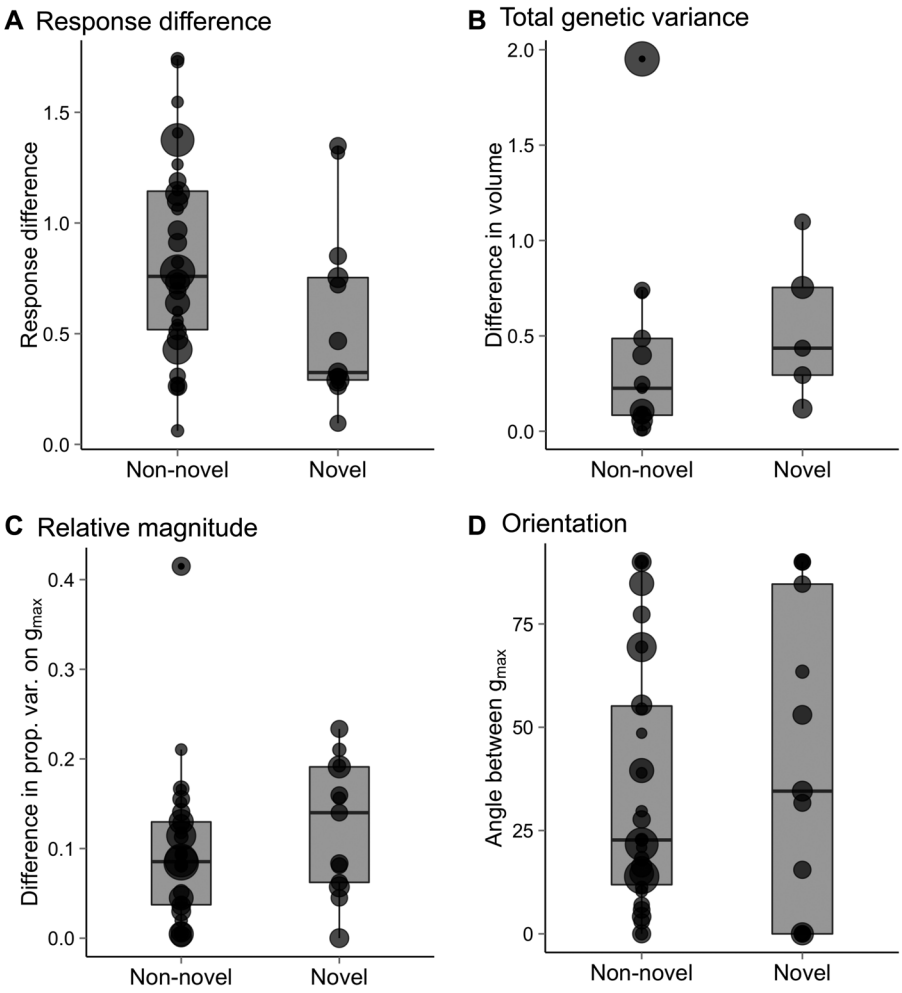

Figure 3. **Box-and-whisker plots of the difference in (A) the predicted evolutionary trajectory and (B–D) the structure of G in comparisons between nonnovel and novel environments. The whiskers extend to 1.5 times the interquartile range. Each datapoint is a single comparison of two G-matrices, scaled by the sample size used to estimate G. See Table 3 for statistics. The results are not qualitatively affected by the removal of the outlier in the upper left corners in panels (B) and (C).**

the strength of selection on the multivariate phenotype (Agrawal et al. 2001). The impact of environmentally induced change in **G** on evolutionary trajectories therefore depends on whether it accumulates over time or is amplified by parallel changes in selection, a question that remains unanswered in the current literature.

Differences in selection among environments complicate inferences about the implications of environmental effects on **G** for evolutionary constraint. Because genetic correlations function as constraints only if they oppose selection (Agrawal and Stinchcombe 2009; Conner 2012), two similar G-matrices can impose very different constraints under different selection regimes. The assumption that selection is constant across environments is inherent in our analysis of differences in the predicted evolutionary trajectory because we applied identical random vectors of selection gradients to the two G-matrices. In heterogeneous environments, however, variation in selection is common (MacColl 2011), and may frequently accompany differences in **G**. If differences in selection among environments amplify small differences in **G**, our approach may underestimate the effect of environmentally induced change in **G** on the evolutionary response, or overestimate it if differences in selection among environments counterbalance differences in **G**.

WHAT DIFFERENCES IN G-MATRIX STRUCTURE UNDERLIE DIFFERENCES IN THE EVOLUTIONARY RESPONSE?

Our analysis suggests that changes in the evolutionary response appear to be primarily due to changes in the orientation of the major axis of variation, which was significantly correlated with the response difference (Table 2). Reorientation of genetic correlations constitutes a major difference in **G**—arguably the most important—because it alters the most accessible direction of evolution and affects sources of indirect selection on each trait (Phillips and Arnold 1999; Arnold et al. 2008). We detected strong

Table 3. Results from general linear models testing the effect of environmental novelty and the median change in mean phenotype on between-environment differences in G.

	Evolutionary trajectory		Structure of **G**					
	Response difference		Total genetic variance		Relative magnitude		Orientation	
	$F_{1,39}$	P	$F_{1,14}$	P	$F_{1,39}$	P	$F_{1,39}$	P
Novelty	0.066	0.798	0.232	0.638	0.000	0.985	0.060	0.808
Number of traits	**14.126**	**<0.001**	0.042	0.841	**4.506**	**0.040**	3.300	0.077
Sample size	3.831	0.057	2.656	0.125	0.012	0.913	0.124	0.727
	$F_{1,29}$	P	$F_{1,15}$	P	$F_{1,29}$	P	$F_{1,29}$	P
Median change in mean phenotype	0.273	0.606	2.054	0.172	0.641	0.430	1.753	0.196
Number of traits	**20.951**	**<0.001**	0.107	0.748	2.742	0.109	0.933	0.342
Sample size	2.270	0.143	**17.332**	**<0.001**	0.364	0.551	1.069	0.310

A separate model was run with each of the four matrix comparison metrics as the dependent variable. Bold entries are significant ($\alpha = 0.05$).

effects of the environment on the orientation of genetic correlations, indicative of common among-environment differences in patterns of phenotypic integration and multivariate genetic constraint. Between-environment differences in **G** exceeded between-population differences for matrices with only a few traits, suggesting that environmental effects on genetic trade-offs between traits can exceed evolved changes due to selection or drift, although the opposite was true for matrices with many traits (Fig. 2D). Our analysis corroborates previous research that provides substantial evidence for environmental effects on genetic variances (Ledón-Rettig et al. 2010; Berger et al. 2011; McGuigan et al. 2011; Clark et al. 2013). There were large differences in total genetic variance between environments that rivaled the differences in total genetic variance between populations (Fig. 2B, Table 1). This heritable variation released by the environment ("cryptic genetic variation"; Ledón-Rettig et al. 2014; Sikkink et al. 2015) is thought to provide a reservoir of standing genetic variation that is exposed under conditions of environmental perturbation, and can contribute to the evolutionary response under new selection regimes (Waddington 1956; Paaby and Rockman 2014; Shaw and Shaw 2014).

The fact that between-environment differences in the structure of **G** are comparable to between-population differences implies that environment-specific allelic effects may be a crucial component of change in genetic architecture over short timescales. Environment-specific allelic effects appear to strongly affect the orientation of **G** and the structure of genetic trade-offs between traits. These results contrast with the current literature on the stability of **G**, which focuses predominately on changing allele frequencies, often minimizing or entirely omitting the role of changing allelic effects (Agrawal et al. 2001; Phillips and McGuigan 2006; Arnold 2008).

It is important to note that our dataset likely overestimates the differences in **G** between environments and between populations due to observation and publication bias. Many studies of environmental effects on **G** in our dataset chose conditions that they expected to weaken or reverse trade-offs between traits, or selected traits based on a priori expectations of environmental responsiveness (e.g., Czesak and Fox 2003; Haselhorst et al. 2011; King et al. 2011). The latter may be especially likely to affect matrices with few traits (Fig. 2). Similarly, studies that performed between-population G-matrix comparisons often chose populations on the basis of large differences between them (e.g., Doroszuk et al. 2008; Bacigalupe et al. 2013). Finally, negative results are less likely to be published (the "file-drawer problem"; Kingsolver et al. 2012), so literature reviews and meta-analyses commonly overestimate effects of interest (Kingsolver et al. 2001; Charmantier and Garant 2005). There is no reason to expect observation and publication bias to affect between-environment and between-population comparisons unequally, so systematic bias is unlikely to influence our comparison of between-environment and between-population differences in **G**.

WHAT ENVIRONMENTAL CONDITIONS CHANGE G?

A striking result from our analysis is the variance in the magnitude of between-environment differences in the structure of **G** and in the predicted evolutionary response (Fig. 2). Given the considerable variation in environmental effects on **G**, characterizing the conditions that cause changes in **G** is necessary to assess the

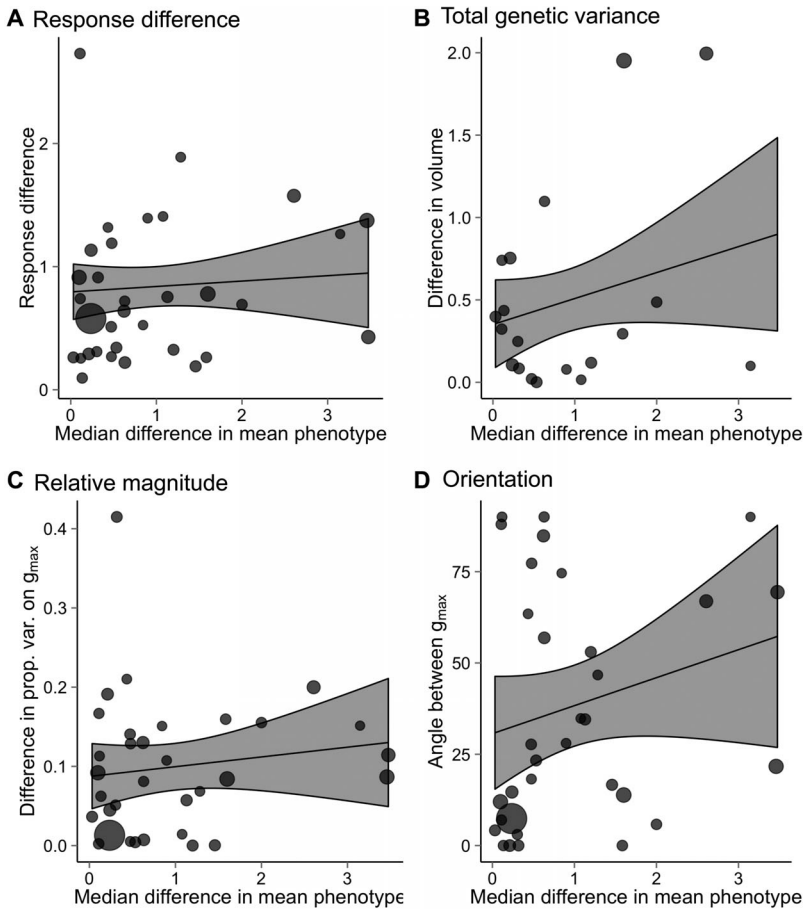

Figure 4. Relationship between the median difference in the mean phenotype and the difference in (A) the predicted evolutionary trajectory and (B–D) the structure of G in the between-environment G-matrix comparisons. Each datapoint is a single comparison of two G-matrices, scaled by the sample size used to estimate G. See Table 3 for statistics, and Methods for details on the calculation of the median difference in the mean phenotype. The results are not qualitatively affected by the removal of the outliers in the upper left corners in panels (A) and (C).

ramifications of environmentally induced change in **G** in natural populations. We found no evidence that the environments with large differences in mean phenotype are associated with large differences in the structure of **G** or the predicted evolutionary trajectory (Table 3 and Fig. 4). This result implies that the environments that induce the largest changes in multivariate genetic architecture have very little impact on univariate phenotypes, and underscores the importance of distinguishing between changes in means and changes in (co)variances when considering responses to the environment.

Novel environments are often implicated in the release of cryptic genetic variation because unfamiliar conditions are expected to disrupt phenotypic buffering mechanisms (Hansen 2006; Paaby and Rockman 2014). Our results do not support this hypothesis (Table 3), although our power to detect an effect was fairly low due to the sample size for this analysis ($N = 44$). Support for this hypothesis in the literature remains equivocal, perhaps because our mechanistic understanding of environmental effects on genetic (co)variance comes primarily from molecular genetics (McGuigan and Sgrò 2009; Ledón-Rettig et al. 2014). It is unclear whether the agents that release genetic variation in the laboratory (e.g., Hsp90; Queitsch et al. 2002) affect quantitative traits in genetically variable populations under realistic ecological conditions (Mittler 2006). A second limitation of our analysis is that we relied on author designations of environmental novelty. This problem is not unique to our meta-analysis. The ubiquity of qualitative rather than quantitative measures of novelty often makes it difficult to reconcile conflicting results from different study systems (McGuigan and Sgrò 2009). Variation in the degree of novelty among studies may have generated enough noise in the data to obscure a relationship between environmental novelty and change in **G**.

FUTURE DIRECTIONS

Our investigation highlights several limitations of the existing data that should guide future research on the nature of environmental

effects on multivariate genetic architecture. First, the current literature is severely taxonomically biased. Plants and insects, two taxonomic groups that are notoriously plastic in response to environmental variation, comprised the vast majority of the between-environment comparisons in our meta-analysis. Studies in other systems are needed to confirm the generality of our results across broad taxonomic groups.

Second, identification of the ecological conditions that are associated with major changes in multivariate genetic architecture is hampered by the absence of an objective metric of environmental difference or novelty, analogous to genetic divergence in among-population comparisons, that is, translatable across study systems. Novelty is often subjectively assessed by individual researchers and frequently conflated with stress, rendering it difficult to isolate the effect of novelty on the genetic architecture of ecologically relevant phenotypes (McGuigan and Sgrò 2009). The absence of such a general predictive framework remains a major constraint on our understanding of the environmental conditions in which labile genetic constraints are likely to impact evolutionary trajectories.

Another valuable avenue of research involves integrating environmental effects on the G-matrix with the environmental variance–covariance (**E**) matrix (Bull 1987; Doroszuk et al. 2008). Together, **G** and **E** jointly determine the phenotypic variance–covariance (**P**) matrix, and therefore the patterns of phenotypic variation and covariation that are visible to selection. Few studies in our meta-analysis reported E- or P-matrices, so we were unable to investigate whether differences in **G** were correlated with differences in **E**, the relationship that ultimately impacts how change in **G** manifests in phenotypic variances and covariances. Future studies investigating the constancy of **E** alongside **G** are necessary to fill this gap (Arnold and Phillips 1999; Doroszuk et al. 2008).

Finally, it is unclear whether the comparison-by-number of traits interaction that we detected in most of our analyses is an artifact of sampling or indicative of a difference in the way that environment-dependent allelic effects and population divergence in allele frequencies impact the G-matrix. One explanation for the pattern we detected is that the environment is more likely to induce changes in the genetic architecture of a small number of highly responsive traits, whereas genetic divergence among populations due to selection and drift results in broader change in genetic architecture across the entire multivariate phenotype. However, our data are unable to discriminate between this hypothesis and sampling bias, and future studies are needed to investigate this possibility.

Conclusion

The short-term stability of genetic constraints remains an unsolved problem in evolutionary biology. Theoretical approaches have produced equivocal results (Walsh and Lynch 2015), and consequently, the stability of **G** has been considered an empirical question for several decades (Turelli 1988; Arnold 2008). In the present study, we demonstrate that environmental effects on genetic architecture can equal or exceed evolved differences in genetic architecture between conspecific populations, although our ability to predict the ecological conditions that precipitate these large changes in **G** remains limited. The evolutionary consequences of this short-term change in **G** depend on whether it represents ephemeral "wobbling" around a mean, or persistent change in the structure of genetic architecture that may shape the evolutionary response in the long term (Walsh and Lynch 2015).

ACKNOWLEDGMENTS

We are grateful to D. Carr, R. Cox, L. Galloway, H. Wilbur, and the Brodie, Cox, and Galloway lab groups for discussions of this manuscript that greatly improved its quality. This manuscript benefitted substantially from comments from A. McAdam and three anonymous reviewers. L. Galloway suggested the comparison between environmental effects on **G** and environmental effects on phenotype means. This work was supported by a Jefferson Scholars Foundation Graduate Fellowship and a National Science Foundation Doctoral Dissertation Improvement Grant DDIG to CWW, and a National Science Foundation grant (IOS-1355003) to EDBIII. We have no conflict of interest to declare.

DATA ARCHIVING

The doi for our data is doi:10.5061/dryad.h95t0

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Associate Editor: A. McAdam
Handling Editor: J. Conner

Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's website:

Appendix S1. List of studies included in the meta-analysis.

Table S1. A Microsoft Excel spreadsheet (.xlsx) containing metadata for the G-matrices used in this meta-analysis, including the species, sample size (number of full- or half-sib families, genotypes, or inbred lines), number of traits, and the environmental manipulation performed.

Table S2. Results from general linear models testing for differences in **G** between environments and between populations ("Comparison" in the table).

Table S3. Results from general linear models testing the effect of environmental novelty and the median change in mean phenotype on between-environment differences in **G**.

Table S4. Results from six general linear models testing for an effect of G-matrix estimation method (narrow or broad sense) on the differences in **G**.

Figure S1. Differences in the predicted evolutionary trajectory (A) and the structure of **G** (B) in between-environment (gray) and between-population (white) comparisons.

Figure S2. Box-and-whisker plots of the difference in (A) the predicted evolutionary trajectory and (B) the structure of **G** in comparisons between nonnovel and novel environments.

Figure S3. Relationship between the median difference in the mean phenotype and the difference in (A) the predicted evolutionary trajectory and (B) the structure of **G** in the between-environment G-matrix comparisons.