

Review

Fluctuating Asymmetry and Steroid Hormones: A Review

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Abstract: Fluctuating asymmetry (FA) represents random, minor deviations from perfect symmetry in paired traits. Because the development of the left and right sides of a paired trait is presumably controlled by an identical set of genetic instructions, these small imperfections are considered to reflect genetic and environmental perturbations experienced during ontogeny. The current paper aims to identify possible neuroendocrine mechanisms, namely the actions of steroid hormones that may impact the development of asymmetrical characters as a response to various stressors. In doing so, it provides a review of the published studies on the influences of glucocorticoids, androgens, and estrogens on FA and concomitant changes in other health and fitness indicators. It follows the premise that hormonal measures may provide direct, non-invasive indicators of how individuals cope with adverse life conditions, strengthening the associations between FA and health, fitness, and behavior.

Keywords: developmental instability; prenatal stress; HPA; cortisol; corticosterone; testosterone

1. Introduction

An organism faces a variety of challenges from its environment during ontogeny. These genetic and external perturbations in the environment leave enduring signs on the adult body. For example, small deviations from perfect symmetry in bilateral traits are highly correlated with the amount of stress experienced during development [1–3]. Potential stressors include extreme temperatures, environmental pollution, predation risk, population density, and inbreeding [4–8]. The small, random imperfections in bilateral symmetry are called “fluctuating asymmetry” (FA), because the direction of the size difference is free to vary [9]. Individuals are presumably buffered against such developmental

insults by employing homeostatic mechanisms to produce the ideal phenotype [10]. Thus, FA is often used as a proxy to quantify developmental stressors and explore the effects of these developmental insults on individuals' health, fitness, and behavior. Indeed, FA increases with exposure to chemical pollutants [7,8,11–14], elevated predation risk [6,14,15], high population density [16,17], and ecosystem disturbances, including extreme temperatures in nonhuman animals [4,13,18–20]. In humans, inbreeding [5], poor health conditions, and various neurological disorders, such as schizophrenia, attention deficit disorder, developmental delays in childhood, and Down syndrome are positively associated with FA [21–25].

Although the adverse effects of developmental stressors on perfect bilateral symmetry are generally acknowledged, the scientific community remains skeptical of FA's widespread use as a proxy for health, fitness and behavior in response to stressors. One important reason for this skepticism is the heterogeneity of the results pertaining to FA and its physiological and behavioral correlates (reviewed in [26–29]). That is, the effect of developmental perturbations on an organism's FA level appears to be trait-, sex-, and stressor-specific and dependent on the developmental stage of the individual [30–33]. One way to carefully assess how various stressors affect morphology is to investigate concomitant physiological changes in the body. For example, human and nonhuman vertebrate animals experience elevated steroid hormone concentrations, namely glucocorticoids in response to stress. Glucocorticoids in turn determine how the body effectively copes with the stressors. These influences may not only affect immediate survival, but future growth, health, and reproduction (reviewed in [34–38]), all implicated as correlates of FA [28]. In addition, sex steroid hormones, namely androgens and estrogens are in part responsible for growth and reproduction [38], and for the observed sex differences in response to stress [38–41]. Several studies also linked androgens and estrogens to FA [42,43]. Surprisingly, very little attention is paid to these neuroendocrine substrates in FA studies and how these substrates may be involved in the development of bilaterally symmetrical characters. Accordingly, the current paper aims to identify possible neuroendocrine mechanisms that may impact the development of asymmetrical characters as a response to various stressors. In doing so, it provides a review of the published studies on hormonal influences on FA and concomitant changes in other health, fitness, and behavioral indicators. It follows the premise that hormonal measures may provide direct, non-invasive indicators of how individuals cope with adverse life conditions, strengthening the associations between FA and health, fitness, and behavior.

The current paper is organized as follows: First, the role of glucocorticoids in individuals' survival, growth, and reproduction is discussed with a brief introduction to neuroendocrine responses to stress. Second, FA studies that implicated major glucocorticoids in the development of bilaterally asymmetrical traits are introduced. Third, the actions of sex steroid hormones on FA are examined. Fourth, empirical findings on the relationship between FA and androgens and estrogens are provided. Fifth, a general summary for the FA and steroid hormone interactions is given. Finally, future directions for this promising area of research are discussed in concluding remarks.

2. Steroid Hormones and FA

2.1. Glucocorticoids

Glucocorticoids are steroid hormones that are vital in regulating metabolic, cardiovascular, homeostatic, and immunological functions. For example, elevated concentrations of corticosterone in response to stressors increase feeding behavior, fat deposition, and mobilization of resources to provide energy [44–47]. Conversely, if an individual cannot effectively cope with chronic or acute stressors, elevated concentrations of glucocorticoids result in impaired immune function, increased mortality, low birth weight [48,49], muscle waste, impairments of cognitive and reproductive function [45–47,50]. Glucocorticoids are secreted in response to a stimulator, namely adrenocorticotropic hormone (ACTH) through the activation of the hypothalamic-pituitary-adrenal (HPA) axis. The HPA axis is a primary regulatory unit of an organism that connects its central nervous system with the hormonal system. Activation of HPA in response to a stressor will result in the secretion of corticotrophin-releasing hormone (CRH) from the hypothalamus. CRH in turn will provoke the release ACTH from the pituitary. ACTH will then stimulate the adrenal cortex and trigger the release of glucocorticoids; cortisol in most primates and corticosterone in most rodents, avian species, and reptiles. The regulation of the HPA axis function is controlled by several negative feedback mechanisms in which glucocorticoids play a major role to ensure the organism's timely return to the equilibrium state [34,36,38].

If glucocorticoids are vital in several physiological functions that affect health, growth, and survival then FA, a proxy for these variables, should also be influenced by glucocorticoids. For example, prenatal stress disturbs the hormonal milieu in the mother and disrupts the HPA function and its response to stressors in both the mother and offspring [51]. Because prenatal stress also increases FA [52–54], extended exposure to glucocorticoids in developing organisms should yield high FA along with other adverse consequences, such as reduced growth and high mortality. The following section reviews empirical findings regarding these conjectures.

2.1.1. Nonhuman Animal Studies

2.1.1.1. Prenatal Development Period

Several investigators have acknowledged the importance of glucocorticoids in studying the relationships among FA, health, growth, and survival. The resulting experiments involved prenatal exposure to corticosterone and concomitant changes in body symmetry in birds. It was found that corticosterone treatment resulted in greater embryonic mortality, reduced growth, and increased FA in tarsus length in chickens and marginally elevated FA of the face length in Japanese quails [55,56]. A separate experiment manipulated cortisol concentrations in embryos of coral reef damselfish and explored the adverse effects on growth and survival. As predicted, high cortisol concentrations in the eggs resulted in increased egg mortality and greater asymmetry in hatchlings [57].

2.1.1.2 Postnatal Development Period

If environmental perturbations during postnatal growth also adversely affect bilateral symmetry [58], and, if an individual cannot effectively cope with these chronic or acute stressors then elevated concentrations of glucocorticoids in response to these stressors should accompany asymmetric developmental trajectory. Indeed, moderate nutritional deficits during post-hatching development elevated baseline corticosterone concentrations in nest-bound Western scrub-jays [59]. Also, one year old scrub jays that experienced nutritional deficits as hatchlings had higher FA in bone and feather measurements compared to controls. The treatment group had also marginally stronger adrenocortical response to acute restraint stress than controls. The results were further corroborated by two studies that investigated two divergent genetic lines of Japanese quail selected for their high (HS) and low stress (LS) plasma corticosterone response to acute restraint stress. It was found that HS quail had significantly greater FA in the lengths of tibiotarsus and metatarsus bones, middle toe, and faces than LS quail [56,60].

Conversely, if animals can effectively cope with potential stressors by showing hyposensitivity to chronic stressors during postnatal development then low glucocorticoid concentrations should be associated with low FA. Indeed, female Siberian hamsters reared in winter-like conditions with short day lengths and low temperatures in the laboratory had significantly lower cortisol concentrations in response to acute stressors and lower FA in adulthood compared to the females that were reared in any other temperature and day length groups [61]. An elevated stress response marked by increased glucocorticoids in winter months may compromise growth, immune, and other important functions that require significant energy reserves [62]. Therefore, energetic adaptations during winter may attenuate physiological stress response as energy shortages in this period may limit the animals' ability to cope with stressors [63]. Accordingly, winter-like conditions during neonatal development may evoke hyposensitivity to stress and enhance ideal growth patterns.

Notably, an experiment that involved studying the relationships among postnatal exposure to heavy metals, food provisioning, and FA produced null results regarding corticosterone concentrations [64]. Specifically, great tit nestlings in a heavy metal polluted area exhibited higher asymmetry of primaries than those in the unpolluted sites. However, no differences in corticosterone concentrations were found between the treatment and control groups. This null result was attributed to the effect of heavy metals on corticosterone activity. Indeed, low level of chronic exposure to heavy metals has been shown to reduce the secretion of corticosteroids in fish and amphibians [65].

2.1.2. Human Studies

Data pertaining to the glucocorticoids and FA in humans are scant and involve only one study. This study assessed the extent to which a natural disaster (*i.e.*, ice storm) experienced by mothers during 14–22 weeks of pregnancy predicted fingerprint ridge count asymmetry in the offspring [66]. Results show that prenatal maternal stress during gestation weeks 14–22 yielded greater dermatoglyphic asymmetry in the offspring. Maternal post-disaster cortisol, however, was negatively correlated with the children's dermatoglyphic asymmetry. Given the small sample size, the results regarding maternal cortisol concentrations should be interpreted with caution as the authors suggest. Only 17 mother-child

comparisons could be made for maternal cortisol and children's finger ridge count asymmetries. It should also be noted that the target group corresponded to the children who were exposed to the ice storm in utero during 14–22 weeks of gestation. Finger ridge configurations are established before the 19th week of gestation, however [61–64]. After this period, injury and caustic substances may reduce the appearance of the ridges, but the original pattern will return unless the skin is damaged considerably [97]. If the target group excluded gestation weeks beyond 19, the results might have been different. Moreover, cortisol sampling was made several months after the exposure to the ice storm. Therefore, the findings on maternal cortisol and dermatoglyphic FA in the offspring require further study.

Taken together, relatively high concentrations of glucocorticoids in nonhuman animals are generally the result of environmental stressors and adversely affect symmetrical development of bilateral characters. Conversely, when an organism shows hyposensitivity to stressors as evidenced by low glucocorticoid concentrations, this may enhance symmetric developmental trajectory. Apart from glucocorticoids, sex steroids, namely androgens and estrogens also play an important role in HPA axis response to stressors. These hormones have also been implicated in several FA studies [73,74]. The following section briefly reviews major functions of androgens and estrogens in relation to the HPA axis, reproduction, growth, and survival. It then discusses the empirical findings on the relationship between FA and androgens and estrogens.

2.2. Sex Steroids

2.2.1. Androgens

Androgens play an important role in fetal sexual differentiation and subsequent development of the body [41]. The primary androgenic hormone, testosterone (T), is responsible for the development of secondary sexual characters and promotion of skeletal growth [41,74]. T is also positively associated with a number of central nervous system disorders [75], increased ectoparasite load and mortality [74,76], and the weakening of some components of the immune system [74,77]. Moreover, T has inhibitory effects on the stress-induced HPA activation [36,37]. For example, ACTH and corticosterone responses to acute stressors are increased with gonadectomy in rodents [77,78]. Castration also increases the ACTH and corticosterone response to various stressors in the rodent [78]. Because almost all of the major functions of T have been correlated with FA [79], several animal studies examined the relationship between T and FA. These relationships focused mainly on secondary sexual character development, such as ornament size and shape in birds and reptiles. These are elaborated upon below.

2.2.1.1. Nonhuman Animal Studies

Ornamental traits are often T dependent. Because T may suppress immune function and increase parasite load and mortality, the expression of such sexual traits is costly [74,80]. Accordingly, high T concentrations that result in species-specific expression of sexual characters should also render an individual at risk for asymmetric developmental trajectory. However, experimental evidence does not support this prediction. For example, experimental manipulation of T induced integumentary head

coloration in the lizard *Psammodes algirus* and concomitantly increased ectoparasite load and mortality [80]. T treatment in this species, however, did not increase nuptial head coloration FA indicating that asymmetry was not affected by the presumable physiological stress induced by T implementation. Similarly, no significant associations were found between tarsi FA and T-dependent frontal shield size and color in moorhens [81].

Apart from sexual character development, androgens are also responsible for skeletal growth. If the actions of androgens can be altered through experimental manipulation during early development then FA of bilateral traits may also be affected indicating developmental stress. One such experiment investigated the effects of embryonic exposure to androgen disrupting chemicals, which alter synthesis, release or actions of androgens, on growth and FA in Japanese quails [82]. Although significant differences in reproductive, immunological, and behavioral measurements were observed between controls and treated animals, exposure to the chemicals did not alter body weight or FA.

2.2.1.2. Human Studies

Human studies mostly focused on the correlational relationships between T and dermatoglyphic asymmetry [72], and, putative markers of T and facial and body FA [73,83–85]. Dermatoglyphic variables were chosen because of their link to developmental variation, their predictable pattern of development during fetal life [86,87] and their association with certain disorders of the central nervous system [87]. Because T is also linked to developmental rate and various neurological disorders [72], a positive association between dermatoglyphic asymmetry and testosterone concentrations was expected. As predicted, high T was associated with high dermatoglyphic asymmetry in males [72].

A putative marker of T, namely digit ratio was also chosen as a parameter of interest because of the reported sex differences and the ease with which this marker is measured. The length of the second digit relative to that of the fourth digit (2D:4D) is generally sexually dimorphic with males having low 2D:4D compared to females. Digit ratio is assumed to be a negative correlate of prenatal T [88], because most mammalian sex differences are androgen dependent [89,90] and digit length markings and bone-to-bone proportions during embryonic and fetal development are comparable to those in adulthood [91]. Because T is responsible for secondary sexual character development (e.g., broad jaws in men), high T concentrations would produce low 2D:4D resulting in low immunocompetence [74] putting the individual at risk for high FA [73]. Indeed, a significant correlation between low 2D:4D and high facial asymmetry in human males, and, high 2D:4D and high facial asymmetry in human females were reported [73]. However, these results should be interpreted with caution. First, the investigators aimed to provide a link between FA of sexual characters, such as broad jaws in men and 2D:4D. However, no specific measurements were made to include these types of characters. Second, it is not clear why a high, typical female 2D:4D should be associated with high facial asymmetry. On the other hand, a second study indicated a curvilinear relationship between body asymmetry and 2D:4D. That is, both low 2D:4D and high 2D:4D were associated with elevated levels of asymmetry, especially in the fingers [83]. However, it has been argued that most of the observed correlations between 2D:4D and degrees of asymmetry are likely to be statistical artifacts and predictions can be formulated contrary to the observed patterns [79,84,85]. Because the same variables (*i.e.*, digits) were used as both dependent and independent variables, U-shaped associations would be

expected [83] even in the absence of any association between 2D:4D and FA, rendering the results spurious [79,84,85]. These conjectures were further corroborated by the observation that 2D:4D in deceased human fetuses and young children correlate neither with finger FA nor any other trait asymmetries [79]. More importantly, it should be noted that no direct evidence exists thus far linking fetal T to 2D:4D.

Taken together, the negative relationship between FA and circulating androgens in human and nonhuman studies is generally not supported by data. When significant associations were found in humans, the mechanisms through which androgens exert their influence on the development of bilateral characters remain unspecified. One exception to this is dermatoglyphic asymmetry. Perhaps because dermatoglyphic characters' phenotypic plasticity is relatively low and thus they are presumably more susceptible to potential stressors this effect may be observed.

2.2.2. Estrogens

Apart from androgens, estrogens are also important for fetal sexual differentiation and subsequent development of the body [41]. Moreover, nonhuman animal studies show a strong stimulatory effect of the sex steroid estradiol on HPA axis functioning [38]. Despite these associations, only a few studies investigated the relationship between estrogens and FA. These studies pertained only to breast FA in women. Because breast development is estrogen dependent and high estrogen concentrations may put individuals at risk for breast cancer, the primary focus was on breast FA and susceptibility to breast cancer [92,93]. These studies indicated high breast asymmetry was indeed a risk factor for breast cancer. Although estrogens' role in breast development and susceptibility to breast cancer were the core arguments in these studies, no direct hormonal measures were taken to confirm the purported associations. Similarly, another study investigated the relationship between breast asymmetry and measures of body size and composition [94]. It was hypothesized that heavy women with high levels of body fat would produce more estrogen and would thus have large breasts resulting in high FA. Although breast asymmetry was positively correlated with body mass and volume, again, no hormonal measures were taken to confirm whether estrogens actually contributed to any of these associations.

Taken together, the empirical evidence supporting the adverse effects of estrogens on FA is scant and indirect. Accordingly, further studies are needed to determine how estrogens may affect the development of bilaterally symmetrical characters, especially in bones. Because, non-fixed asymmetries in soft tissue traits may show a cyclical pattern as a result of changing hormone concentrations [95,96], inclusion of characters that are not affected by short-term fluctuations in hormone concentrations would serve as better indicators of health or fitness. It should also be noted that the primary androgenic hormone, T, can exert estrogenic effects after being metabolized to estrogen by aromatization [38]. Therefore, current studies involving sex steroid hormones do not provide sufficient depth to evaluate positive or deleterious effects of androgens and estrogens on FA [72].

3. Summary

FA in bilateral morphological characters often indicates an organism's inability to effectively cope with stressors in the environment. Because the associations between FA and health, fitness, and

behavior appear to be trait-, sex-, and stressor-specific, FA's widespread use as a measure for growth and survival is disputed [26–29]. If stress-induced changes in the phenotype are accompanied by such physiological measures as elevated concentrations of stress hormones then the purported associations between FA and growth and survival are unlikely to be spurious. Accordingly, the current paper attempted to provide an overview of the published studies pertaining to steroid hormone-FA interactions. In doing so, it focused on glucocorticoids. Glucocorticoids' important functions in regulating the stress-activated HPA axis, consequently growth, reproduction, and survival [38] constituted the bases of these discussions. Further emphasis was also given to sex steroid hormones because of their role in maintaining the ideal developmental trajectory, and, androgens' inhibitory and estrogens' stimulatory effects in stress-induced HPA activation [36–38].

This review indicated that high glucocorticoid concentrations, namely cortisol and corticosterone generally have deleterious effects on ideal growth patterns and survival in nonhuman animals. The evidence regarding the deleterious effects of glucocorticoids on FA in humans remains unspecified, however. Similarly, the mechanisms through which androgens exert their influence on bilateral asymmetry are unidentified in both humans and nonhuman animals. Finally, the associations between estrogens and FA are at best indirect and pertain only to breast FA in women, thus require further study.

4. Concluding remarks

There is a promising area of research concerning neuroendocrine substrates and their relationship with the achievement of ideal developmental trajectory. The associations between exposure to stressors and deviations from bilateral symmetry can be strengthened by employing non-invasive, easy-to-collect physiological measures both in the laboratory and the field. Because very little attention is paid to stress-hormone-FA interactions in the otherwise vast FA literature, future research would greatly benefit from attempts to close this gap.

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