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The stress response systems: Universality and adaptive individual differences ☆

Bruce J. Ellis [a,*], Jenée James Jackson [a], W. Thomas Boyce [b]

[a] *John and Doris Norton School of Family and Consumer Sciences, University of Arizona, P.O. Box 210033, Tucson, AZ 85721-0033, USA*
[b] *School of Public Health/Institute of Human Development, University of California, Berkeley, USA*

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Abstract

Biological reactivity to psychological stressors comprises a complex, integrated system of central neural and peripheral neuroendocrine responses designed to prepare the organism for challenge or threat. Developmental experience plays a role, along with heritable variation, in calibrating the response dynamics of this system. This calibration occurs through setting of response thresholds in the regulatory mechanisms that coordinate the expression and use of trait-specific gene products and environmental elements that build alternative phenotypes. Whereas natural selection tends to favor developmental plasticity when the fitness of alternative phenotypes can be predicted from observable cues, genetic polymorphisms are most likely to be maintained when the advantages of niche specialization are high and organisms can evaluate and select their niches. Well-developed theories of both adaptive phenotypic plasticity and adaptive genetic variation in the stress-response systems have been advanced in the literature. Taken together, these theories strongly suggest that variation in stress-response phenotypes has been shaped by natural selection, is an adaptation to multiniche environments, and involves an integration of genetic influences and condition-sensitivity.

Keywords: Stress reactivity; Stress physiology; Ontogeny; Evolutionary psychology; Phenotypic plasticity; Molecular genetics; Behavior genetics

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* Corresponding author.
E-mail address: bjellis@email.arizona.edu (B.J. Ellis).

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The stress response systems comprise a complex, integrated network of central neural and peripheral neuroendocrine responses designed to prepare the organism for challenge or threat (reviewed in Boyce & Ellis, 2005). While this network has a core structure that all humans share, there are large and enduring differences between people in the magnitude of their stress responses. Indeed, some individuals incur powerful biological responses to relatively minor stressors, while others experience little change from baseline in response to even major, life-altering events; some are visibly shaken by challenge or threat, while others appear behaviorally unaffected; and some sustain—as a consequence of their biological reactions to stress—inordinately frequent or severe medical difficulties, while others are largely immune to the health-eroding effects of adversity.

What are the causes and functions of this variation? At a proximate level, how do genes and environment influence the regulatory mechanisms that guide development of characteristic levels of stress reactivity (referred to herein as *stress-response phenotypes*)? At an evolutionary level, how has the process of natural selection organized these regulatory mechanisms? Is variation in these mechanisms underpinned by adaptive genetic variation, maintained in equilibrium by natural selection, enabling individuals with different stress-response phenotypes to thrive in a multiniche environment? And what is the role of condition-sensitivity, that is, sensitivity to developmental experience? Are these regulatory mechanisms conditional adaptations that monitor specific features of childhood environments as a basis for calibrating stress-response phenotypes to adaptively match those environments? Or are impinging genetic and environmental influences on the stress response systems random and non-adaptive, creating functionless noise in an otherwise functional system?

In this essay, we articulate a framework for addressing these questions. We begin with a review of the species-typical neurobiology of the human stress response systems (human nature) and the broad variability in the reactivity of these systems across persons (individual differences). Both the human nature and individual differences components of these systems develop through complex interactions between genetic and environmental influences. We then discuss ecological conditions that favor the maintenance of adaptive genetic variation and adaptive phenotypic plasticity and review criteria for identifying these types of adaptations. Alternative phenotypes are most likely to be maintained by natural selection in multiniche environments that afford different ways for individuals to survive and reproduce. Next we present a theoretical model, based on West-Eberhard (2003), for conceptualizing genetic, environmental, and structural influences on development of alternative phenotypes. Central to this model is the concept of genetically and environmentally sensitive regulatory mechanisms that control patterns of gene expression underpinning alternative developmental pathways. The West-Eberhard model then guides our discussion of adaptive genetic variation and adaptive phenotypic plasticity in the stress response systems.

In these final sections, we review (a) a theory of adaptive genetic variation in the stress response systems and associated behavioral phenotypes proposed by Korte, Koolhaas, Wingfield, and McEwen (2005), (b) a theory of adaptive phenotypic plasticity in the stress response systems and developmentally linked defensive and reproductive strategies in rodents proposed by Cameron et al. (2005), and (c) a theory of adaptive phenotypic plasticity in the human stress response systems and associated biobehavioral outcomes proposed by Boyce and Ellis (2005). Taken together, these theories strongly suggest that variation in stress-response phenotypes has been shaped and maintained by natural selection, and that this adaptive variation involves an integration of genetic influences and con-

dition-sensitivity. We conclude by considering proximate and evolutionary models that could potentially account for this dual genetic and environmental regulation.

Levels of genetic influence on the stress response systems

A full understanding of neurobiology of the human stress response systems involves identification of both their species-typical, universal structure (human nature) and systematic variation in the reactivity of these systems (individual differences). Both the human nature and individual differences components of stress reactivity develop through complex interactions between genetic and environmental influences (Boyce & Ellis, 2005). In terms of genetic influences, the vast majority of the human genome is identical across individuals; that is, 99.9% of chemical nucleotide bases are exactly the same in all humans[1] (Human Genome Project, 2001). This shared genetic structure, in interaction with species-typical environments, underlies the development of universal features of the human anatomy, physiology, and psychology. At the same time, 0.1% of the human genome varies between individuals. Although this may seem miniscule, the human genome contains approximately 3.2 billion nucleotide bases (i.e., the four chemical bases—adenine, thymine, cytosine, and guanine—that pair to build DNA). Accordingly, a recent study of human genetic variation reported 9.2 million candidate single nucleotide polymorphisms (SNPs), of which 2.4–3.4 million have been validated using multiple techniques[2] (International HapMap Consortium, 2005). SNPs, together with microsatellite mutations, are the most common and widely distributed classes of mutations that produce variation across DNA sequences, that is, allelic variations. These two types of small-scale mutations are thought to make up the bulk of human genetic diversity and potentially impact phenotypic trait variation.

Complex adaptations require the coordinated expression of large numbers of genes during development. Many of these genes possess different alleles at given loci. When these allelic variations are neutral with regard to fitness outcomes (i.e., when they were not structured by natural selection and are not relevant to the development and functioning of the adaptation), the resulting adaptation is considered to have a genetically monomorphic structure. In this paper, we assume that the human nature component of the stress response systems has a genetically monomorphic structure.

Individual differences in the reactivity of the stress response systems emerge through various forms of gene–environment interaction. One form of interaction is phenotypic plasticity: the presence of a monomorphic genetic structure within a species that systematically biases individuals toward development of different phenotypes in response to distinct environmental conditions. Another form of interaction is between allelic variations across individuals and environmental conditions. In this case, phenotypic variation results from individuals with different genotypes encountering different environments and/or responding differently to the same environments. For example, allelic variations may moderate relations between childhood experiences, such as maltreatment, and developmental outcomes, such as expression of a conduct disorder (Caspi et al., 2002; Caspi, Sugden, Moffitt, Taylor, & Craig, 2003). As discussed below, the presence of genetic variation does not

[1] The estimate of human genetic similarity is based on the reference sequence constructed by the Human Genome project, which is informative about the number of bases that are invariant across individuals.

[2] The estimate of human genetic variation is based on the reference SNP map conducted by the International HapMap Project, which is informative about DNA sequence variation among individuals.

imply adaptation. Indeed, only a small percentage of the existing genetic variation is likely to have been structured and maintained by natural selection (Hughes & Burleson, 2000).

Different disciplines within the biological sciences have often taken different perspectives on the importance of genetic variation for determining human individual differences. Evolutionary psychologists, for example, have traditionally argued for a universal human nature that emerges from a genetically monomorphic structure (Tooby & Cosmides, 1990, 1992). Accordingly, evolutionary psychologists have often minimized individual differences in genetic structure and emphasized phenotypic plasticity in response to different environments as the primary mechanism for adaptive individual differences. Genetic variation from this perspective is regarded as the raw materials upon which natural selection operates rather than as a product of natural selection that functions to adaptively structure traits during development. Behavioral geneticists, by contrast, have been primarily concerned with understanding how genetic variation among individuals translates into meaningful individual differences in behavior. Although quantitative and molecular genetics have focused on estimating heritable variation and identifying important allelic variants, distinguishing between adaptive variation and non-adaptive variation has not been a priority. Despite these disciplinary tendencies to either downplay or emphasize the role of genetic variation, recent theory and data suggest that adaptive individual differences are likely to be the product of both genetic and environmental regulation, as discussed below.

The human nature component of the stress response systems

Following Bjorklund, Ellis, and Rosenberg (in press), the term human nature is used to denote phenotypic traits that reliably develop in a species-typical manner when individuals possess the underlying monomorphic genetic structure (i.e., no disruptive mutations) and experience a species-typical environment during their development. By this definition, the stress response systems have a major human nature component. Indeed, the primary stress response axes, as well as their central and peripheral components, appear early in phylogeny and have been extensively conserved in the evolutionary history of vertebrate and mammalian species (Bentley, 1998; Nilsson & Holmgren, 1994).

The neurobiology of the human stress response systems can be characterized at a species-typical level: Environmental events signaling threats to survival or well being produce a set of complex, highly orchestrated responses within the neural circuitry of the brain and peripheral neuroendocrine pathways regulating metabolic, immunologic, and other physiological functions. This elaborate and tightly integrated repertoire of responses results in a shift to a state of biological and behavioral preparedness, involving increases in heart rate and blood pressure, metabolic mobilization of nutrients, preferential redirection of energy resources and blood to the brain, and the induction of vigilance and fear. The neural basis for the organism's stress response comprises two anatomically distinct but functionally integrated circuits: the corticotrophin releasing hormone (CRH) system and the locus coeruleus–norepinephrine (LC–NE) system (Chrousos, 1998; McEwen, 1998; Meaney, 2001). Co-activation of the these two systems, along with their linkages to emotion regulatory brain regions such as the amygdala, the anterior cingulate cortex, and the prefrontal cortex, produce the coordinated biobehavioral changes associated with the stress response in mammalian species.

The CRH system comprises two distinguishable subsystems, one centered in the paraventricular nucleus (PVN) of the hypothalamus and involved in the homeostatic regulation of the hypothalamic–pituitary–adrenocortical (HPA) axis, and the other involved in the

circuitry of the amygdala and its connections. Within the former subsystem, CRH is released into the portal blood supply of the pituitary in a circadian fashion by neurons in the PVN and serves as the primary trigger for production of pro-opiomelanocortin (POMC) polypeptide by the anterior pituitary. In the second subsystem, CRH cell bodies are more widely represented in areas outside the hypothalamus, including the amygdala (a component of the limbic system with known roles in aggression and fear reactions), the substantia innominata (part of the basal forebrain and involved in the maintenance and regulation of attention), the bed nucleus of the stria terminalis (a neural projection from the amygdala to the ventromedial nucleus of the hypothalamus, thought to mediate appetitive behaviors), and in the prefrontal, insular, and cingulate regions of the cortex (cortical areas involved in emotion regulation and the activation of behavioral and neuroendocrine responses to stress and challenge) (Gold & Chrousos, 2002; Owens & Nemeroff, 1991).

Two or more types of CRH receptors have been found: CRH_1 receptors in the anterior pituitary and other brain regions, which are involved in generating fear-related behavior; and CRH_2 receptors that seem to play a counter-regulatory role in anxiety. POMC is cleaved into its component proteins, corticotrophin (ACTH) and β-endorphin (Smith et al., 1998), and ACTH is transported in plasma to the adrenal cortex, triggering secretion of cortisol, the principal human glucocorticoid regulating blood pressure, glucose metabolism, and immune competence. Circulating cortisol adaptively regulates the activation level of the HPA axis through a process of feedback inhibition at the hypothalamus, the pituitary, and centers outside the hypothalamus, such as the hippocampus and prefrontal cortex (Dallman et al., 1987). Contexts characterized by social-evaluative threat, particularly when the threatening conditions are uncontrollable, are especially likely to elicit a significant cortisol response (Dickerson & Kemeny, 2004).

The LC–NE system comprises the noradrenergic cells of the brainstem and their projections to the amygdala, hippocampus, mesolimbic dopamine system, and the prefrontal cortex (Aston-Jones, Rajkowski, Kubiak, Valentino, & Shipley, 1996). LC activation of hypothalamic centers contributes to activation and regulation of the autonomic nervous system (ANS), initiating the so-called 'fight or flight' responses to challenge. The ANS, comprising sympathetic, parasympathetic, and enteric branches, modulates physiologic arousal and recovery in the periphery and produces the familiar biological signs of stressful encounters, including heart rate and respiratory rate acceleration, sweat production, dry mouth, and, if sufficiently severe, loss of urinary or fecal continence. These biological responses are mediated both by direct autonomic innervation of target organs and by secretion of catecholamines by the adrenal medulla.

Though anatomically distinct, the functioning of the CRH and LC–NE systems is highly integrated and cross-regulatory. CRH-expressing neurons in the amygdala, for example, project directly to the LC, escalating the firing rate of LC neurons, enhancing NE release, and producing many of the fear-related behaviors associated with stressful experience (Meaney, 2001; Valentino, Curtis, Page, Pavcovich, & Florin-Lechner, 1998). These CRH-mediated pathways from the amygdala to the LC may also underlie many of the symptoms of anxiety disorders, such as acoustic startle responses, vigilance, symptoms of avoidance, and recurrent emotional memories. Reciprocally, activation of NE secreting neurons in the LC has been shown to increase CRH production in the PVN (Habib, Gold, & Chrousos, 2001). This cross-regulatory process is only one of several ways in which the LC–NE and CRH are functionally interactive (Gold & Chrousos, 2002; Viau, 2002). Taken together, these systems are the primary physiological, homeostatic means by which

survival under threat is protected, but are also among the dysregulatory pathways by which psychologically and emotionally relevant environmental signals result in the behavioral, autonomic, and immunologic manifestations of human pathology (Cacioppo et al., 1998; Heilig, Koob, Ekman, & Britton, 1994; McEwen & Stellar, 1993).

The LC–NE and CRH systems appear early in phylogeny, showing both genetic expression and comparable biological functions in multiple animal species from invertebrates to primates. These systems comprise a complex, highly interactive repertoire of central and peripheral stress responses, which together mobilize neurobiological and behavioral resources in defense of the organism's integrity and well being. Although these neurobiological responses are protective and essential in acutely stressful conditions, they can become themselves pathogenic when persistently activated under circumstances of chronic or overwhelming stress and adversity.

The individual differences component of the stress response systems: Evolutionary perspectives on variation

Although the neural circuitry and peripheral neuroendocrine pathways that comprise the human stress response systems have a shared species-typical structure, there is great variation between individuals in the reactivity of these systems to external stressors. Reactivity has been defined as "the deviation of a physiological response parameter from a comparison or control value that results from an individual's response to a discrete, environmental stimulus" (Matthews, 1986, p. 461). Broad individual variation in reactivity to psychological stressors has been documented in human adults (Cacioppo et al., 1998), human children (Alkon et al., 2003; Allen & Matthews, 1997), and both young and mature laboratory animals (Meaney, 2001; Suomi, 1987). As reviewed by Boyce and Ellis (2005), several important conclusions about the origins of individual differences in stress reactivity have emerged from the human and animal literatures: First, it is now well-established that allelic variation, environmental factors, and their interaction contribute to calibration of the major stress response systems—the CRH and LC–NE systems—over the course of early development (e.g., Barr et al., 2004; Cameron et al., 2005; Higley et al., 1993). Second, stable individual differences in these systems emerge with maturation, with a subset of both human (Cacioppo, Berntson, Sheridan, & McClintock, 2000) and non-human primate (Suomi, 1997) populations showing extreme or prolonged activation of one or both systems. Third, there is pronounced early plasticity in the neurobiological mechanisms that underpin the development of the CRH and LC–NE systems, and aspects of early experience, particularly parent–child experiences, appear to play a central role in the calibration of stress responses (Hofer, 1994; Meaney, 2001). Fourth, ongoing exposure to familial and ecological stressors can cause changes in the set-points of the CRH and LC–NE systems, resulting in either hyper- or hypo-reactivity of these neuroendocrine pathways (e.g., Barr et al., 2004; Flinn, this issue; Flinn, Quinlan, Turner, Decker, & England, 1996).

What are the evolutionary origins of broad and enduring individual differences in reactivity of the stress response systems? One possibility is that this variation is simply random and non-adaptive (i.e., evolutionary noise), much as differences between people in the length of their toes is random and non-adaptive, owing to selection-irrelevant genetic variation, the random effects of sexual recombination, and non-adaptive phenotypic plasticity in response to experience. Such variation could still be heritable and somewhat predictable in response to environmental factors, but it would not be the product of natural selection and would have

had little bearing on fitness in ancestral environments. Along these lines, theory and data from evolutionary quantitative genetics suggest that most genetic variation is due to non-adaptive or neutral forces such as mutation-selection balance (Hughes & Burleson, 2000). Further, neutral and non-functional forms of phenotypic plasticity have been documented. For example, prenatal cocaine exposure results in hyper-reactivity of the LC–NE system and hypo-reactivity of the CRH system in human infants (reviewed in Mayes, 2002). These alterations of the stress response systems caused by neurotoxic intrauterine exposure represent disruptions of normal developmental processes rather than adaptive phenotypic plasticity.

Another possibility is that variation in reactivity of the stress response systems is adaptively patterned (within species-typical developmental environments). If this were the case, then different levels of stress reactivity should produce mean differences in survival and reproductive outcomes when all individuals are constrained to a single environment, but these differences should diminish when different reactivity phenotypes are allowed to covary with salient features of the environment, that is, when individuals with different reactivity profiles can employ strategies and inhabit niches that are matched to those profiles (see Mealey, 2001). A quasi-experimental study of the effects of stress reactivity under varying environmental conditions in rhesus monkeys suggests that individual differences in stress reactivity may meet these criteria. The troop of macaques, which had been previously assessed for their degree of biobehavioral reactivity to novel or challenging stimuli, lived in a 5-acre wooded habitat in rural Maryland. In 1993, the troop encountered a 6-month period of protective confinement to a small, 1000-square foot building, during a construction project on the habitat grounds. During this confinement period, when behavioral strategies available to troop members were severely curtailed, highly reactive monkeys suffered dramatically higher rates of violent injuries than did their less reactive peers (see Fig. 1). In the free-ranging wooded habitat, however, where a wide range of behavioral strategies could be employed, including escape from conflict, highly reactive monkeys suffered comparatively low rates of violent injury (Boyce, O'Neill-Wagner, Price, Haines, & Suomi, 1998).

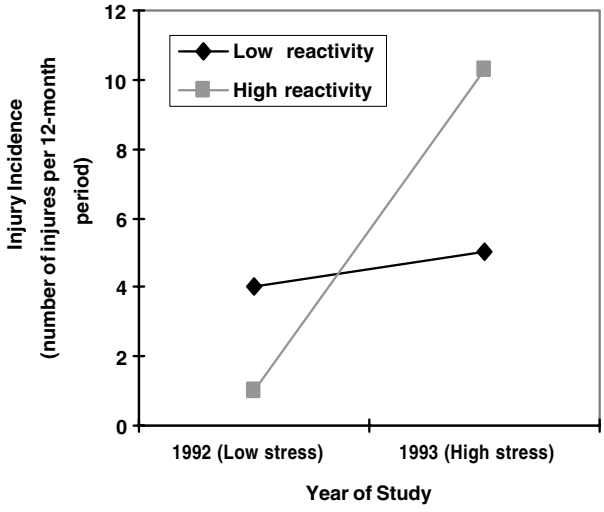


Fig. 1. Effects of alternative stress-response phenotypes on morbidity varies across socio-ecological conditions. Shown here is the cross-over interaction between biobehavioral reactivity and confinement stress in prediction of injury rates in a troop of semi-free ranging rhesus monkeys ($N = 36$) (redrawn from Boyce et al., 1998).

Natural environments are often complex and afford more than one way to survive and reproduce. Such multi-niche environments provide the ecological basis for the evolution of adaptive phenotypic variation within species. This adaptive variation can evolve in response to the physical diversity of environments (i.e., ecological niches that vary over time or space) or as alternative solutions to problems of social competition. The survival and reproductive strategies of the bluegill sunfish (*Lepomis macrochirus*) provide an example of both types of adaptive variation. Bluegill inhabit a spatially heterogeneous physical environment, occupying both the littoral (i.e., shoreline) and open-water zones of freshwater North American lakes. Bluegill in these different niches diverge in ways that are obviously functional: Bluegill that inhabit the open-water environment tend to be more fusiform and have smaller pectoral fins that minimize drag, whereas bluegill inhabiting the littoral zone of the same lake tend to be deeper-bodied and have larger pectoral fins that enable them to maneuver through their spatially complex environment (Ehlinger & Wilson, 1988).

In addition, the breeding system of bluegills is complex and affords males with three pathways to reproductive success (Gross, 1982). There is a "parental" pathway in which males mature at a large body size and aggressively defend territorial positions and build nests in breeding colonies. Then there are "sneaker" and "mimic" pathways in which males mature at a small body size and dash in to spawn simultaneously with the parental male when the female releases eggs in his nest. Sneakers gain access by their small size, whereas mimics gain access by imitating the appearance and courtship behavior of females. Neither sneakers nor mimics build nests. The relative fitness of these three male strategies presumably varies as a function of such factors as the sex ratio in the population, the frequency of each strategy in the population, local ecological conditions (e.g., predation pressures and their effects on between-strategy variation in mortality), and the relative competitive abilities (e.g., health, vigor, age, and learning ability) of individual males.

In complex, multiniche environments, where selection is unlikely to converge on a single "best" phenotype, and where the fitness of alternative phenotypes is predictable on the basis of observable environmental cues, selection tends to favor adaptive phenotypic plasticity. Indeed, phenotypic plasticity is very common in nature, can be irreversible (i.e., fixed) or reversible (i.e., labile) during the lifetime of an organism, enables individuals to function as generalists or become specialized to a particular niche, enables adaptive coordination with environmental conditions, and can persist over the long-term without equal fitness payoffs (West-Eberhard, 2003). At the same time, however, there are potentially high costs of phenotypic plasticity (e.g., producing and maintaining the appropriate regulatory and assessment mechanisms for alternative development; see DeWitt, Sih, & Wilson, 1998); thus, in some cases genetically based polymorphisms will be selected for instead. Such polymorphisms are likely to be favored by selection when advantages of niche specialization are high (Wilson, 1994), when organisms can evaluate and select their niches (Wilson, 1994), and when reliable environmental cues for entraining or switching between alternative phenotypes do not exist (West-Eberhard, 2003). For genetic polymorphisms to be maintained by natural selection, they must evolve toward a state of equilibrium in which the average fitness of the alternative alleles are equal. Despite these conditions favoring either adaptive genetic variation or phenotypic plasticity, virtually all carefully studied phenotypic variants have been found to be both condition-sensitive and influenced by genetic variation (West-Eberhard, 2003).

Genetic, environmental, and structural influences on development of alternative phenotypes: The West-Eberhard (2003) model

West-Eberhard (2003) provides a useful framework for conceptualizing the proximal development of alternative phenotypes via regulatory switch mechanisms, which serve as a transducer of genetic, environmental, and structural influences on phenotypic variation. Central to her model is the concept of a developmental switch point: "A point in time when some element of phenotype changes from a default state, action, or pathway to an alternative one—it is activated, deactivated, altered, or moved" (p. 67). In Fig. 2, West-Eberhard presents diagrammatically the genetic architecture of switch-controlled alternative phenotypes. The model distinguishes between phenotypic regulation (the switch) and form (expression of alternative traits controlled be the switch). The determinants of phenotypic regulation include genetic (r) and environmental (e) inputs that contribute to the threshold (T) response of a given regulatory mechanism (R). Once a threshold is passed, the regulatory mechanism coordinates the expression and use of trait-specific gene products and environmental elements that build either phenotype A or B.

As an illustration of this process, we describe the developmental event of gonadarche using the West-Eberhard framework. Gonadarche is a switch point in human development that is regulated by the hypothalamic–pituitary–gonandal (HPG) axis. The HPG axis first develops and is temporarily active during periods of prenatal and neonatal development. Gonadarche is the secondary reactivation of the HPG axis after a period of relative quiescence during childhood. Specifically, gonadarche begins at approximately 9 or 10 years of age in girls and soon thereafter in boys with the reactivation of pulsatile secretion of

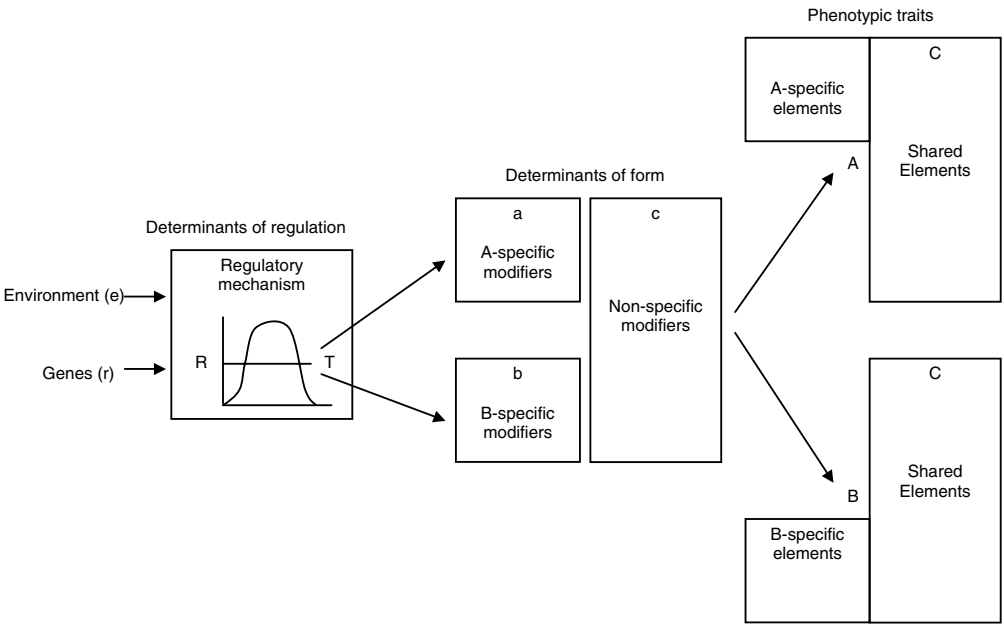


Fig. 2. Schematic diagram of the genetic architecture of switch-controlled alternative phenotypes. The model distinguishes between determinants of phenotypic regulation (the switch) and determinants of form (expression of alternative traits controlled be the switch) (from West-Eberhard, 2003).

gonadotropin-releasing hormone (GnRH). GnRH is produced by neurons in the hypothalamus and causes the anterior pituitary to synthesize and secrete biologically potent gonadotropins: luteinizing hormone (LH) and follicle-stimulating hormone (FSH). At gonadarche, pulsatile secretion of LH and FSH markedly increases. This causes a cascade of events. In girls, this cascade includes ovarian follicular development, increased production of ovarian steroid hormones, development of secondary sexual characteristics, peak height velocity, menarche, subcutaneous fat deposition, widening of the pelvis, and ultimately establishment of cyclic ovarian function—all of which culminates in maturity of the female reproductive system (see Ebling, 2005; Grumbach & Styne, 2003; Plant & Barker-Gibb, 2004, for overviews of the neurophysiology of puberty).

As shown in Fig. 2, a switch point is controlled by a condition-sensitive, quantitatively variable regulatory mechanism (R) with threshold (T). In the case of gonadarche, the neurotransmitter and neuromodulatory systems that control the GnRH secretory network are the coordinating regulatory mechanism. Appropriate pulsatile secretion of GnRH—small pulses every 60–90 min—is the threshold that must be passed for the developmental switch to occur. The normal curve in Fig. 2 represents the timing (i.e., age distribution) of the developmental switch in the population; for gonadarche, the mean around which this normal distribution occurs is 9 or 10 years of age in girls (as noted above). In terms of pubertal development, gonadarche can be thought of as a master switch, with subsequent decision points working as subordinate switches in a developmental sequence. The regulatory mechanism is the locus of operations for genetic (r) and environmental (e) influences on timing of gonadarche. These genetic and environmental influences ("modifiers of regulation") influence the value of T (level of pulsatile release of GnRH) and/or the organism's ability to pass T. In the case of gonadarche, the regulatory mechanism is influenced by allelic variations (e.g., Barker-Gibb, Plant, White, Lee, & Witchel, 2004; Weintrob et al., 2000), environmental factors such as stress and nutrition (reviewed in Ellis, 2004), and extant phenotypic characteristics that modulate the mechanism's functioning and sensitivity (e.g., metabolic efficiency, energy stores, leptin concentrations, and efficiency of hormone-secreting organs). Importantly, these three forms of influence are hierarchically organized: The preexisting phenotype is the transducer of both genetic and environmental sources of information (West-Eberhard, 2003), and the modified phenotype retains these changes as development proceeds. The developmental switch—gonadarche—initiates a cascade that, in an unfolding developmental sequence, determines patterns of gene expression that underlie pubertal maturation. Sequences of developmental switches and resultant gene actions cause developmental linkage of coexpressed sets of genes (see West-Eberhard, 2003).

Although gonadarche is a universal developmental event, timing of gonadarche varies widely across and within populations. Moreover, timing of gonadarche is one component of a correlated suite of reproductive characteristics. Specifically, girls who experience earlier gonadarche and pubertal development, compared with their later maturing peers, tend to have higher levels of serum estradiol and lower sex hormone binding globulin concentrations that persist through 20–30 years of age; have shorter periods of adolescent sub-fertility (the time between menarche and attainment of fertile menstrual cycles); experience earlier ages at first sexual intercourse, first pregnancy, and first childbirth; and tend to be fatter and heavier in adolescence and early adulthood (reviewed in Ellis, 2004; St. George, Williams, & Silva, 1994; van Lenthe et al., 1996).

In the life history literature, this covariation between timing of puberty and related morphological, neuroendocrine, and behavioral characteristics is conceptualized as alternative

reproductive strategies (i.e., alternative phenotypes that evolved together as coadapted, functional sets; see Figueredo et al., this issue). In terms of Fig. 2, we will refer to the early pubertal developmental pathway as Phenotype A and the late pubertal developmental pathway as Phenotype B. As West-Eberhard has stated, "The regulatory mechanism coordinates the expression and use of *specific modifier* gene products and environmental elements (a, b) that compose phenotype A or B but are not used in both" (p. 67). Thus, depending on the timing of the developmental switch (gonadarche), certain patterns of gene expression differ in Phenotype A and Phenotype B. At the same time there are nonspecific modifiers (c): gene products and environmental elements involved in pubertal development that are shared by (expressed in) both Phenotype A and Phenotype B but are not affected by the timing of gonadarche. In sum, Phenotypes A and B are subunits of gene expression or gene-product use; i.e., the coordinated expression of these phenotypes—their linkage as coexpressed traits—are subunits of gene action. This gene action is determined by the timing of the developmental switch, which is co-determined by impinging environmental and genomic information.

Although the West-Eberhard (2003) model diagrammatically represents the architecture of discrete, switch-controlled alternative phenotypes, discrete traits (i.e., qualitative or discontinuous variation) are relatively rare in nature; instead, phenotypic variation is almost always continuously distributed (Reznick & Travis, 1996), as is timing of pubertal development. Gonadarche is a discrete developmental switch point, but value of T and the organism's ability to pass T varies across individuals as a function of allelic variations and environmental influences. Allelic influences on gonadarche, as in virtually all complex traits, are polygenic and thus bias the population toward a continuously variable distribution of phenotypes (West-Eberhard, 2003). Likewise, manifold environmental influences on regulatory mechanisms produce continuous phenotypic variation. Taken together, these multiple genetic and environmental influences produce the normal distribution in the regulatory mechanism box depicted in Fig. 2. Finally, although some switches explicitly control expression of discrete phenotypes (e.g., sex determination), in the case of normally distributed phenotypic traits that are subject to multiple allelic and environment influences, switches occur between successive causal events in a developmental pathway.

Genotype-specific regulation of complex alternative phenotypes

As specified by the West-Eberhard (2003) model, differences between alternative phenotypes within a population result primarily from differences in gene expression, not differences in gene frequencies (such as those found in genetically divergent populations). Allelic variations influence differences in gene expression through their effects on developmental switches. In terms of understanding allelic influences on regulation of complex alternative phenotypes, therefore, the key issue is how different alleles affect switch mechanisms.

Traditionally, adaptive alternative phenotypes have been treated as genetic polymorphisms. Genetic polymorphism refers to the presence of two or more alternative alleles that exist at a single-locus and influence a developmental switch in a rather simple Mendelian fashion (Futuyma, 1998). Given that complex adaptive alternatives are almost always the product of multiple genes acting in concert to influence a switch mechanism, the traditional concept of genetic polymorphism for a trait can be rather misleading. Within the context of polygenic regulation, the threshold responses of developmental switches are subject to continuously variable genetic and environmental influence.

If single-locus influence on a developmental switch is demonstrated, it most often occurs in the context of other "background genes" that are present in all individuals. Human sex determination is a suitable example. Sex is determined by the presence or absence of a single gene, the H–Y antigen on the Y chromosome (Bull, 1983). In spite of this, the H–Y antigen gene does not contain the information necessary for building a male or female system. Instead, the genetic subsystems for males and females are present in all individuals, and the genes on the Y-chromosome have only a regulatory effect on the switch threshold that initiates a polygenic cascade leading to the development of sexually organized systems. Accordingly, West-Eberhard (2003) has argued that such cases of genetic polymorphism are more accurately described as *genotype-specific*. Genotype-specific regulation means that one of several alleles that influence a switch mechanism predominates over others (and over environmental factors) in the magnitude of its effect and thus has a decisive impact on phenotypic determination.

However, genotype-specific regulation that is immune to environmental influence is rare in nature. Instead, genotypes have *reaction norms*—the range of phenotypes that will be developed by a genotype in different environmental contexts (Schlichting & Pigliucci, 1998). Along these lines, most presumed examples of genetically regulated complex alternatives have proven to have condition-sensitive regulation, that is, genotype-phenotype relations have been found to vary predictably as a function of environmental context. For example, alternative mating behaviors found among male swordtail fish (*Xiphiphorus nigrensis*) are often cited as an example of complex alternatives that are produced by a single-locus polymorphism (e.g., Cook, Compton, Herre, & West, 1997; Gross, 1996; Ryan, Pease, & Morris, 1992). In the swordtail, three alleles at the *P* locus on the Y chromosome correspond to three modes in size distribution of mature males (small, intermediate, and large; Ryan et al., 1992). Although all three genotypes perform the range of species-typical mating strategies, they do so at different size-related frequencies. Specifically, small, intermediate, and large males generally sneak, sneak and court, and court females respectively. Size is the primary mediating mechanism in this species through which allelic variations influence mating strategies.

As in the preceding example of human puberty and related variation in reproductive strategies, the key developmental switch in male swordtail fish is gonadarche. Specifically, the three alleles at the *P* locus differentially influence timing of gonadarche (e.g., immunoreactive GnRH-containing neurons first appear at 5 weeks of age in genotypically small males versus 11 weeks of age in genotypically large males; Rhen & Crews, 2002). In addition to these allelic influences, timing of gonadarche is also sensitive to a number of environmental factors, such as temperature (Borowsky, 1987a) and agonistic interactions with other males (Borowsky, 1987b). These environmental influences can result in genotypically small males that are larger than genotypically intermediate males, and alternative mating strategies correlate more strongly with size than with genotype (Ryan & Causey, 1989). In addition, mating strategies of male swordtail fish are competition-dependent in relation to interaction with other males. For example, males of intermediate size will sneak and chase females rather than court when in the presence of larger males.

In sum, both genomic and environmental factors influence timing of gonadarche, which in turn coordinates patterns of gene expression involved in the developmental cascade that induces sexual maturation and halts or dramatically reduces growth. Timing of gonadarche strongly influences size, and size is a major developmental factor in entrainment of alternative mating strategies. At the same time, mating strategies are facultatively adjusted

in response to current physical and social dimensions of the environment. Thus, although there are strong genotypic influences on size and developmentally linked mating strategies, the development of the alternative phenotypes in fact emerges through a complex series of gene–environment interactions. Such interactions are virtually universal in development (West-Eberhard, 2003).

The stress response systems: An evolutionary model of adaptive genetic variation

A model of adaptive genetic variation in the stress response systems and developmentally linked behavioral phenotypes has been proposed by Korte et al. (2005). This is an overarching model that is based on a wide range of animal literatures and is not specific to a single species. Korte et al. (2005) posit that natural selection has maintained allelic variation for two phenotypic patterns of neurobehavioral development within populations: high-aggression Hawks and low-aggression Doves. Both phenotypes can be successful, the model contends, but under different environmental conditions. An implicit assumption of the model is that alternative stress-response phenotypes are encompassed by higher-order variation in Hawk–Dove strategies.

The evolutionary Hawk–Dove model of maintenance of alternative phenotypes

Adaptive alternative phenotypes that are thought to be underpinned by genetic variation are frequently conceptualized as evolutionarily stable strategies. An evolutionarily stable strategy (ESS) is one that cannot be bettered (invaded) by an alternative strategy, once most members of a population possess it. Evolutionary game theory models attempt to demonstrate how a balance of alternative phenotypes can be maintained by natural selection.

Hawk–Dove is a game within the domain of mathematical game theory that models the maintenance of two alternative fighting strategies (Maynard Smith, 1982). Hawks represent a strategy characterized by escalation of fighting until either injured or the opponent retreats. Doves on the other hand, display to the opponent and then retreat at once if the opponent escalates the fight. If a Hawk encounters another Hawk, then they will fight until one is seriously injured. If a Dove encounters another Dove, then they will display until one of them tires and decides to move on. However, if Hawk and Dove meet then the Hawk will most certainly win the fight. Each of these strategies is not evolutionarily stable on its own. For instance, in a population of all Doves, a mutant Hawk can invade the population and reap large pay-offs. Similarly, in a population of all Hawks, the Hawk strategy becomes very costly and a mutant Dove would possess a higher average fitness pay-off. Therefore, over evolutionary time, a stable ratio of Hawks and Doves within populations should evolve through frequency-dependent selection.

The Hawk–Dove model favored by Korte et al. (2005) is based heavily on the programmatic work of Dingemanse, Drent, van Oers, and colleagues on personality variation in great tits (*Parus major*) (Dingemanse, Both, Drent, & Tinbergen, 2004; Dingemanse, Both, Drent, van Oers, & van Noordwijk, 2002; Dingemanse, Both, van Noordwijk, Rutten, & Drent, 2003; Drent, van Oers, & van Noordwijk, 2002; van Oers, de Jong, Drent, & van Noordwijk, 2004; reviewed in Groothuis & Carere, 2005). Great tits display enduring individual differences in a correlated set of personality traits that broadly map onto the Hawk–

Dove continuum. Birds on the hawkish end of the continuum tend to be aggressive and bold in exploring their environment, but do so in a superficial way. These fast-superficial explorers take more risks in fighting, are quicker to approach novel objects and conspecifics (e.g., quicker to explore new trees, to attack an intruder, to approach a member of the opposite sex), and are more likely to become founders of new colonies than their dovish peers. Birds on the dovish end of the continuum, by contrast, are less likely to attack an intruder and instead engage in more prolonged threat displays (which facilitates information gathering about an opponent prior to a confrontation). Employing a more passive strategy, Doves are relatively unaggressive and shy in exploring their environment, but do so in a more thorough manner. These slow-thorough explorers tend to be more sensitive to external stimuli and behaviorally responsive to changes in their environment than their hawkish peers. Variation in these Hawk–Dove personality traits in great tits have demonstrated moderate heritability (van Oers, de Jong, van Noordwijk, Kempenaers, & Drent, 2005).

Covariation between the Hawk–Dove dimension of personality in great tits and fitness in fluctuating environments provides an empirical basis for a model of adaptive genetic variation in Hawk–Dove strategies. Inhabiting forests in Europe and Asia, great tits are territorial and non-migratory. In the studies conducted in The Netherlands, these birds experience unpredictable ecological changes (stochastic variation in the severity of winters), which greatly impacts food supply (presence vs. absence of mast seeding beeches), which in turn strongly influences survival rates, physical condition at fledging, population density, and intrasexual competition for territories and mates. In bad years, when food is scarce, Dingemanse et al. (2004) found a positive correlation between hawkishness in females and survival. The hawkish personality afforded an advantage when competing for sparse, clumped resources. By contrast, in good years, when food was abundant, there was a strong negative correlation between hawkishness in females and survival. Hawkish behavior apparently resulted in increased mortality at a time when conspecific aggression had no benefit. The opposite pattern emerged in males. Male great tits devote much effort to defending territories. In good years, although food competition is relaxed, there is increased competition for territories because population density increases. These conditions favor hawkish males, who more aggressively and successfully expel intrasexual competitors from their territorial space. By contrast, in bad years when food is scarce and populations contract, there is little competition for territories. Male Doves have markedly higher survival rates in this context than do male Hawks. The authors suggest that this is because the Doves avoid costly aggressive encounters, which have little adaptive value when territories are not a limiting resource (Dingemanse et al., 2004).

In total, just as bluegill sunfish inhabit a multiniche environment that varies across space (i.e., littoral vs. open-water zones), great tits inhabit a multiniche environment that varies across time. Multiple niches are produced by stochastic variation in climate cycles, and the fitness costs and benefits of being a Hawk or a Dove are niche-specific. The fluctuating climate cycles, through their effects on food supplies and intrasexual competition, result in density-dependent selection for Hawks and Doves, but in opposite directions in good and bad years and in males and females. Given the advantages of niche specialization and the absence of reliable environmental cues for predicting annual climate change, natural selection maintains adaptive genetic variation in the population for Hawk–Dove strategies (as would be predicted by bet-hedging models of the maintenance of alternative

phenotypes; see Seger & Brockmann, 1987).[3] These adaptive gene combinations appear to be further maintained across generations by assortative mating among great tits on Hawk–Dove personalities (Groothuis & Carere, 2005). In sum, the great tits provide a model of how genotypic variation underlying Hawk–Dove strategies could be maintained by natural and sexual selection. The heritability data on variation in Hawk–Dove phenotypes (van Oers et al., 2005) are consistent with this model.

Genotypic regulation of alternative Hawk–Dove phenotypes

Korte et al. (2005) have applied the basic Hawk–Dove model to their analysis of alternative phenotypic strategies. They argue that natural selection has maintained a balance of alternative phenotypes preserving genes for Hawk–Dove variation in a wide range of animal populations. Korte et al. conceptualize the Hawk–Dove dimension as encompassing not only variation in behavioral phenotypes (e.g., bold-shy, aggressive-unaggressive, impulsive-cautious, and risk-prone vs. risk-averse), but also underlying structural differences in neurobiology and systematic variation in the reactivity of the CRH and LC–NE systems (Fig. 3).

As specified by the West-Eberhard (2003) model, development of complex alternative phenotypes is regulated by switch mechanisms that are subject to continuously variable genetic and environmental influences. In the case of genotype-specific regulation, one of several alleles that influence a switch mechanism predominates over others (and over environmental factors) in the magnitude of its effect on downstream phenotypic outcomes. Korte et al. (2005) assume this type of allelic influence on Hawk–Dove phenotypes (Fig. 3). This assumption has been supported by artificial selection experiments, which provide strong evidence of genetic influence on variation in Hawk–Dove strategies in birds and rodents (Groothuis & Carere, 2005; van Oers et al., 2005). These selection line experiments and other related heritability studies, however, have not identified the relevant allelic variations. Nonetheless, van Oers et al. (2005) suggest that polymorphisms in the dopamine 4 receptor gene (DRD4) and the serotonin transporter gene (5-HTT) could influence variation in Hawk–Dove strategies (see Fig. 3).

The physiological functions of the D4 receptor remain unclear, making it difficult to ascertain how DRD4 variants differentially relate to dopaminergic functioning (for a review see Oak, Oldenhof, & Van Tol, 2000). However, there is some evidence that the long and short forms of the receptor protein have modest functional significance in terms of their pharmacologic binding properties (Asghari et al., 1994) and inhibition of cyclic adenosine monophosphate (Asghari et al., 1995). In terms of variation in Hawk–Dove strategies, individuals that possess long alleles of the DRD4 gene display greater novelty seeking (impulsive, exploratory, sensation-seeking behavior) than those that possess short alleles (Benjamin et al., 1996; Ebstein et al., 1996). Further, many studies have demonstrated linkage between the long allele of DRD4 and attention deficit hyperactivity disorder (ADHD), a disorder characterized by inattention, hyperactivity, and impulsivity (Levine, 1999).

In addition, a functional polymorphism (5-HTTLPR) in the promoter region of the serotonin (5-HT, 5-hydroxytryptamine) transporter gene could also be viewed as influencing Hawk–Dove strategies through its covariance with anxiety, fearfulness, and related

[3] An analogous evolutionary model of the maintenance of genetic variation in Hawk–Dove strategies has also been proposed for bighorn sheep, based on stochastic variation in predation pressures (Réale & Festa-Bianchet, 2003).

Dove Strategy

Hawk Strategy

• ? Short-repeat allele in the promoter region of the serotonin transporter gene
•? Short alleles of DRD4 gene

Allelic Variation

• ? Long-repeat allele in the promoter region of the serotonin transporter gene
•? Long alleles of DRD4 gene

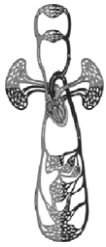
• ↓Glucocorticoid receptor expression
• Morphologically better developed hippocampus
• ↓Negative feedback sensitivity;
•↑ CRH expression
•↑ Basal serotonin neurotransmission

Neurobiological Structures

•↑ Glucocorticoid receptor expression
•↑ Dopaminergic reactivity in nigrostriatal system
• ↓Basal serotonin neurotransmission

•↑ HPA responses to stressors
• ↓Sympathetic adrenomedullary reactivity
•↑ Th2 humoral immunity; adaptive for parasites
•↑ Vulnerability to stress-induced illness

Stress Physiology



•↑ Sympathetic adrenomedullary reactivity to stressors
• ↓ACTH and corticosterone reactivity
•↑ Testosterone and DHEA
• ↓Parasympathetic responsivity
•↑ Th1 cellular immunity; adaptive for infection, but risks inflammation and autoimmune disease
•↑ Resistance to stress-induced illness over lifespan

• More fearful behavior
•↑ Freeze-hide
•↑ Sensitivity to external stimuli; monitoring of environment for dangers
• ↓Aggression; exploration; risk-taking

Adaptive Variability in Behavior

• More bold, aggressive behavior
•↑ Fight or flight
• ↓Abilities to organize environmental information and incoming sensations
•↑ Incidence of risky and violent behavior

Fig. 3. Genotypic regulation of alternative Hawk–Dove phenotypes: A model of adaptive genetic variation in the stress response systems and associated behavioral phenotypes. DRD4, dopamine 4 receptor gene; CRH, corticotrophin releasing hormone; HPA, hypothalamic–pituitary–adrenocortical; ACTH, corticotrophin; Th1, T Helper 1; Th2, T Helper 2; DHEA, dehydroepiandrosterone.

behaviors (Caspi et al., 2003; Champoux et al., 2002; Kremer et al., 2005; Lesch et al., 1996). Serotonin transporters are presynaptic proteins that affect the clearance of neurotransmitter from the synaptic cleft following vesicular release in serotonergic neural circuits. A short (*s*) repeat allele is associated with low transcriptional efficiency compared to

the long (*l*) repeat allele, resulting in diminished expression of 5-HTT and lower 5-HT reuptake into the presynaptic neuron. At the level of behavior, individuals with the *s* allele display greater anxiety and fearfulness, more easily acquire conditioned fear responses, and adopt cautious behavior in novel environments (Hariri et al., 2002; Murphy et al., 2001). Such functional variation in 5-HTT may also figure largely in the phenotypic expression of stress reactivity and biological sensitivity to stressful or threatening social contexts. Hariri et al. (2002, 2005) have reported, for example, that human subjects carrying the *s*-allele of 5-HTTLPR exhibit increased amygdala responses to fearful stimuli on fMRI, compared with subjects homozygous for the *l* allele. Finally, central nervous system serotonergic responsivity has been linked to variation in impulsiveness and aggression (reviewed in Manuck, Kaplan, & Lotrich, 2004).

DRD4 and 5-HTT are just two of many candidate genes that could influence Hawk–Dove phenotypes through their effects on neurotransmitter synthesis, recognition, reuptake, release, and degradation. Whatever the relevant allelic influences on the regulatory mechanisms that control development along the Hawk–Dove phenotype continuum, these mechanisms are certain to be condition-sensitive as well and to support phenotypic plasticity. For example, an early defining feature of the Hawk phenotype in great tits is aggressive sibling competition for food: Hawkish nestlings more persistently and intensively solicit their parents for food than do their dovish siblings (Groothuis & Carere, 2005). However, under conditions of food rationing, dovish nestlings increase their frequency of food solicitations and shift toward a mode of fast-superficial exploration of their environment. Hawkish nestlings become even more aggressive under these conditions (Groothuis & Carere, 2005).

Following the West-Eberhard (2003) model, alternative Hawk and Dove phenotypes are subunits of gene expression or gene-product use; i.e., the coordinated expression of these phenotypes—their coherence as coexpressed traits—are subunits of gene action. This gene action is controlled by regulatory mechanisms, which are co-determined by impinging environmental and allelic information (of which Korte et al. emphasize the latter). Different patterns of gene expression underlying Hawk–Dove phenotypes are manifest in differences in neurobiological structures and stress physiology (see Fig. 3). As summarized by Korte et al. (2005), the classical fight or flight strategy that characterizes the Hawk behavioral phenotype is subserved by systematic differences in patterns of stress reactivity and central neurobiology. Hawks display, for example, vigorous activation of the sympathetic adrenomedullary system and increased testosterone and dehydroepiandrosterone (DHEA) production by the hypothalamic–pituitary–gonadal axis when confronted with challenging or threatening situations. Hawks show, however, comparatively diminished adrenocortical and parasympathetic reactivity under similar circumstances. Such systematic differences in stress biology are found in the hawkish members of a number of species, including great tits, fish, chickens, and rodents. Further, such profiles of stress physiology and reactivity are linked *upstream* to differences in central neural structures and circuitry and *downstream* to differences in the immune functions influenced by stress hormones. Thus, in humans with more hawkish phenotypes, the hippocampus would be expected to be less well developed and serotonergic circuitry to show low tonic 5-HT neurotransmission, resulting in relative diminutions in anxiety, but susceptibility to impulse control disorders. Such a biobehavioral profile is consistent thus far with several studies of children with ADHD or with predispositions to risk-taking and aggressive behaviors (Kruesi et al., 1990; Levitan et al., 2002; Raine, 2002). Physiologically downstream, the immunologic profiles of Hawks

are dominated by T Helper 1 (Th1-type) patterns of cytokine expression, enhanced cellular immune responses to wound infections, but—as a consequence—greater vulnerability to inflammatory and autoimmune processes (Korte et al., 2005).

By comparison, the dovish behavioral phenotype—with its predisposition to fearful behavior and freeze-hide endangerment strategies—is associated with exaggerated HPA axis responsivity, higher stress-related levels of cortisol expression, and relatively diminished sympathetic adrenomedullary activation. These patterns of neuroendocrine response are accompanied by better morphological development of the hippocampus and related advantages in the organization, processing of, and sensitivity to incoming sensory and contextual information. Doves, due to their predilections toward exploring the environment for new resources during periods of food scarcity, are at higher risks of acquiring parasitic infections and show T Helper 2 (Th2) dominated patterns of humoral immune responses. These immunological biases place Doves in a better position to respond effectively to parasite loads but may increase susceptibility to common viral and bacterial infections.

As reviewed by Korte et al. (2005), these differences in the physiology, neuroendocrinology, and neurobiology of Hawks and Doves underpin their divergent behavioral strategies (Fig. 3). These behavioral differences—high vs. low aggression; low vs. high sensitivity to external stimuli and monitoring of environments for danger; fast and superficial vs. cautious and thorough exploratory behavior; fight-flight vs. freeze-hide—enable Hawks and Doves to successfully inhabit specialized niches that, as a result of stochastic variation in ecological conditions and density of competitors, fluctuate unpredictably across time and space.

Environment-specific regulation of complex alternative phenotypes

The Hawk–Dove model proposed by Korte et al. (2005) emphasizes adaptive genetic variation in the stress response systems and associated behavioral phenotypes. However, it is now well-established that not only allelic variation, but also environmental factors and the interaction between genes and environment contribute to calibration of the major stress response systems during development (e.g., Barr et al., 2004; Boyce & Ellis, 2005; Cameron et al., 2005; Higley et al., 1993). It is important, therefore, to also consider carefully the role of phenotypic plasticity—environment-specific regulation of alternative paths of phenotypic development—in the ontogeny of individual differences in reactivity of the LC–NE and CRH systems.

Adaptive phenotypic plasticity has several core characteristics. First, the fitness of alternative phenotypes must be predictable on the basis of reliable cues that can be observed by the individual. Relevant cues include both external environmental factors (e.g., predation pressures, quality of parental investment, seasonal change, diet) and indicators of the individual's status or relative competitive abilities in the population (e.g., age, body size, health, history of wins and losses in agonistic encounters) (Gross, 1996; West-Eberhard, 2003). Second, individuals must develop and maintain the necessary sensory and regulatory machinery—sensory organs, neural pathways, endocrine systems, genetic architecture—to detect and encode these cues and then respond to them in a timely manner (at least during developmental periods of phenotypic readiness to respond).

Third, natural selection organizes the response (phenotypic plasticity) to promote fitness in variable environments; i.e., the response enables matching of the phenotype to conditions where it is expressed. At a proximate level, this response involves a conversion

from one state to another. This conversion can be permanent (*polyphenisms*) or reversible (*polyethisms*). The caterpillar *Nemoria arizonaria* provides an example of polyphenism. These animals have evolved physiological mechanisms that register features of diet in the first three days of life as a basis for permanently activating alternative morphologies (flower vs. twig morphs in spring and summer, respectively). The caterpillar's polyphenism is part of a predator-defense adaptation, which functions to match morphology (camouflage) to predictable seasonal variations in floral feeding ecology (see Greene, 1989, 1996). Polyethisms are environment-specific phenotypes in which more than one alternative can be expressed by the same individual over time. These facultative adaptations constitute fluid phenotypic responses to changing environmental stimuli such as season (e.g., summer to winter morphological changes), noxious substances (e.g., adaptability and plasticity of the immune system), and social context (e.g., facultative adjustment of social strategies).

Fourth, as specified by the West-Eberhard (2003) model, environmental factors influence phenotypic development through their effects on switch mechanisms that regulate gene expression. Although a specific phenotypic alternative may be determined by a small number of environmental cues that influence a relevant developmental switch, the concept of pure environment-specific regulation can be misleading. Specifically, even if phenotypic alternatives are primarily due to environmental effects, this does not mean that a population is genetically uniform in its propensity to adopt one phenotype over another. For example, in certain populations of mice and vols, photoperiod has a major effect on the switch mechanism that regulates hibernation. Nonetheless, a small percentage of individuals still breed in winter (Gorman, Goldman, & Zucker, 2001).

Finally, the evolutionary circumstances for the maintenance of conditional alternatives are much broader than those for genetic polymorphism. Equal fitness among alternative phenotypes is not a necessary condition (Dominey, 1984). As reviewed by West-Eberhard (2003), in many cases natural selection favors a primary phenotype that yields high payoffs under favorable circumstances and a secondary phenotype that "makes the best of a bad situation." For example, the human stress response systems are characterized by adaptive phenotypic plasticity, with early adversity biasing their combined effects toward a profile of heightened or prolonged reactivity. High reactivity phenotypes function in this context to increase the overall capacity and readiness of individuals to deal with very real dangers in their environment; however, these phenotypes also result in chronic overarousal that erodes physical and mental health (Boyce & Ellis, 2005). Despite these costs, the highly reactive phenotypes can be maintained in the population along with normatively reactive phenotypes without achieving equal fitness. This is because the secondary phenotype (high reactivity) only needs to be superior to the primary phenotype (normative reactivity) in a delimited set of environmental and social niches that recurred over evolutionary time. If a switch mechanism evolves so that a secondary phenotype is facultatively produced or performed when it is more advantageous than the primary phenotype (e.g., exaggerated reactivity in dangerous environments), then the secondary phenotype and the regulatory architecture underlying it can be maintained by natural selection.

The stress response systems: An evolutionary model of adaptive phenotypic plasticity

Adaptive phenotypic plasticity in the stress response systems has been perhaps most elegantly illustrated in the programmatic work of Meaney and colleagues at McGill University, Montreal. This work examines how early physical and social environments produce

alterations in parent-offspring interactions, which in turn calibrate the development of stress-responsive neural circuits and regulate reproductive behavior. Building on the early observations of Levine and others (Levine, 1994) and using a rodent model, the Meaney laboratory has systematically characterized a cascade of behavioral, physiological, and epigenetic events through which phenotypic variation in offspring behavior is guided by ecological parameters within physical and social rearing environments (Meaney, 2001; Meaney & Szyf, 2005; Weaver et al., 2004) (see Fig. 4). Such ecological stressors as the presence of predators, infectious disease, and maternal–infant separations interact with

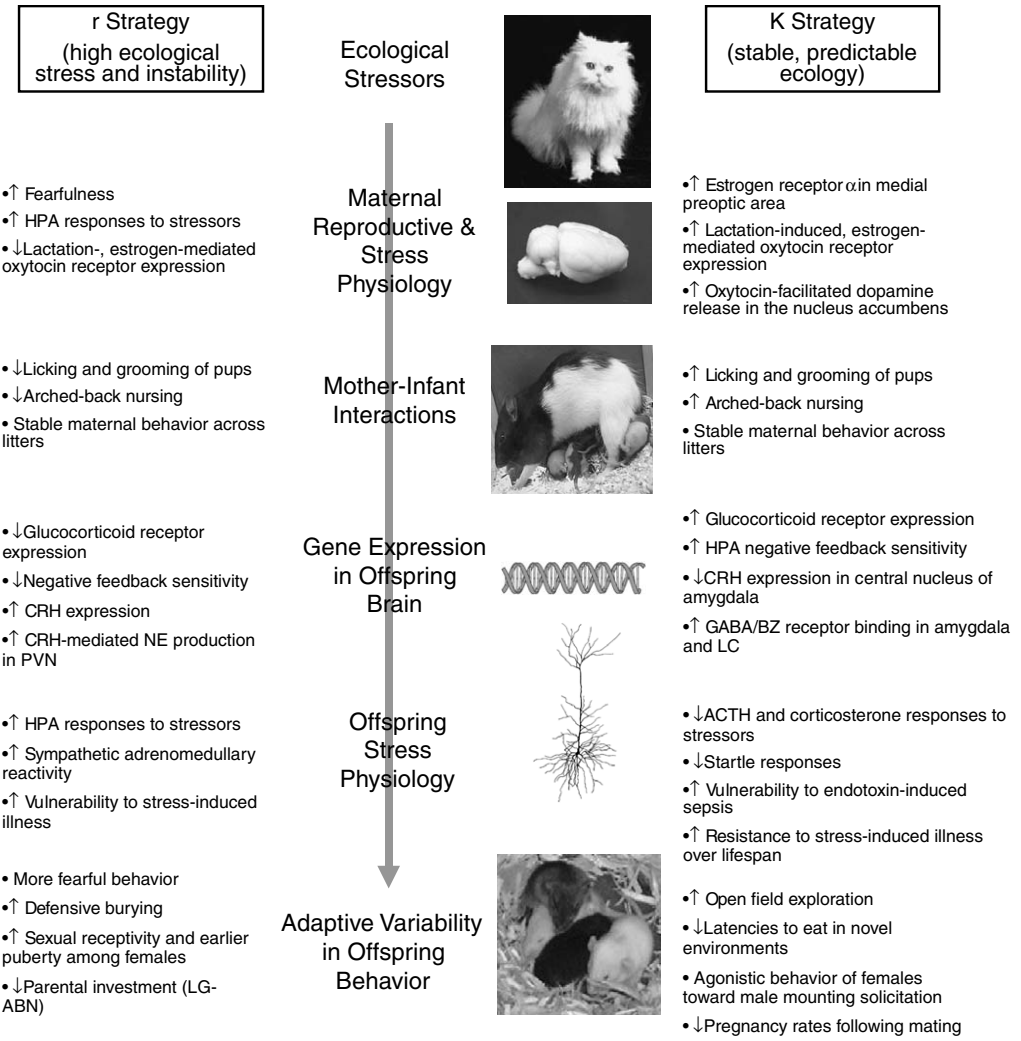


Fig. 4. A theory of adaptive phenotypic plasticity in the stress response systems and developmentally linked defensive and reproductive strategies in rodents. HPA, hypothalamic–pituitary–adrenocortical; CRH, corticotrophin releasing hormone; NE, norepinephrine; PVN, paraventricular nucleus; LG–ABN, licking and grooming-arched back nursing; GABA/BZ, γ-aminobutyric acid/benzodiazepine; LC, locus coeruleus; ACTH, corticotrophin.

heritable differences in maternal reproductive and stress physiology to produce robust differences in the character and frequency of maternal-infant interactions. Such interactions, Meaney and colleagues have shown, are capable of calibrating the differential expression of genes in the infant's central neural circuitry: *epigenetic* differences that then determine lifelong disparities in offspring stress physiology and the adaptive variability in behavior that follows from such disparities. Meaney and colleagues frame their work on adaptive phenotypic plasticity in the context of life history theory.

Life history theory: An evolutionary model of development of alternative phenotypes

The key units of analysis in life history theory (Charnov, 1993; Roff, 1992; Stearns, 1992; see also Figueredo et al., this issue) are life history traits: the suite of maturational and reproductive characteristics that define the life course (e.g., age at sexual maturity, adult body size, time to first reproduction, interbirth interval, level of parental investment, number of offspring). Life history theory attempts to explain correlated variation in life history traits in terms of evolved trade-offs in distribution of metabolic resources to competing life functions: growth, maintenance, and reproduction. These trade-offs are inevitable because metabolic resources are finite, and time and energy used for one purpose cannot be used for another. For example, resources spent on growth and development (e.g., later age at sexual maturity, larger adult body size, increased social quality and competitiveness) cannot be spent on current production of offspring; thus, the benefits of a prolonged development are traded off against the costs of delayed reproduction. Life history theory posits the existence of phenotypic mechanisms that actually make these trade-offs by selecting between or "making decisions" about alternative ways of distributing resources (Chisholm, 1999). Natural selection favors switch mechanisms that, in response to ecological conditions, trade-off resources between growth, maintenance, and reproduction in ways that recurrently enhanced inclusive fitness during a species' evolutionary history.

In conceptualizing overarching differences in life history strategies, it is instructive to compare r-selected species, which preferentially allocate metabolic resources to reproduction, with K-selected species, which bias metabolic resources toward growth and maintenance:[4]

> r-selected species evolved under unstable and unpredictable conditions, leading to a strategy focusing on the *production* of genetically similar individuals (offspring quantity). Rabbits, for example, exhibit rapid sexual development, high fertility, low parental investment, high infant mortality, low interbirth interval, short lives, generally small size, less group cohesion, and less competition for resources because, historically, they evolved under unstable conditions where short-term strategies paid off. Conversely, K-selected species evolved under stable and predictable conditions, leading to a strategy focusing on the *survival* of genetically similar individuals (offspring quality); thus they do not generally exceed the carrying capacity of their environment. Elephants, for example, exhibit slow, delayed sexual development, low fertility,

[4] r and K represent terms of the logistic equation relating population growth to density relative to some carrying capacity and, thus, are best interpreted as terms specific to density-dependent selection. Given that density-dependent selection is but one model of life history trade-offs, it has been argued that classifying complex life history traits as being r- and K-selected is too limited (see Roff, 2002 & Stearns, 1992 for a review of the problems surrounding use of the r–K continuum). Here we use the terms as heuristics only, and remain agnostic to the exact mode of selection responsible for coordinated life history traits and their potential trade-offs within species.

> high parental investment, low infant mortality, high interbirth interval, greater longevity, generally large size, high group cohesion, and intense competition for resources because, historically, they evolved in stable environments where long-term strategies paid off (Figueredo et al., 2005, p. 1351).

An assumption of life history theory is that the same divergent environmental conditions that favor the evolution of r-selected versus K-selected reproductive strategies between species also favor the development of alternative reproductive strategies within species (see also Figueredo et al., this issue). In this paper we will use the symbols r and K as heuristics to refer to alternative reproductive strategies within populations that roughly approximates variation on the r–K continuum. Various life history theorists have hypothesized that ecological stress and instability (e.g., fluctuating resources, high mortality rates) undermines quality of parental investment, and these low investment cues in turn bias offspring toward development of more r-based strategies (e.g., earlier sexual development and mating, lower parental investment, greater *quantity* of offspring). By contrast, more stable ecologies (e.g., predictable resources, low rates of premature death) support higher quality parental investment, and these high investment cues in turn bias individuals toward development of more K-based strategies (e.g., delayed sexual development and mating, higher parental investment, higher *quality* of offspring) (Belsky, Steinberg, & Draper, 1991; Chisholm, 1999; Ellis, 2004).[5]

Environment-specific regulation of stress physiology and associated reproductive strategies in rodents

Within Meaney's model of epigenetic development in rodents, two patterns of phenotypic variation—representing opposing poles along a spectrum of neurobehavioral development—are rough approximations of the r and K life history strategies. Ecological stress and instability and resulting low-quality parental investment impact regulatory mechanisms in offspring that guide development of high physiological and behavioral reactivity to stressors and reproductive precocity. Such conditional adaptations may promote vigilance for environmental dangers and early opportunities for mating and reproduction, typical of more r-selected reproductive strategies. Conversely, more stable ecological conditions that support higher quality parental investment may foster the opposite pattern of development, producing more K-selected reproductive strategies (see Fig. 4). This structured matching of phenotypes to environmental conditions—adaptive phenotypic plasticity—has human analogs in the observations of exaggerated stress reactivity (Felitti et al., 1998; Heim & Nemeroff, 1999) and precocious pubertal development and sexual activity (Ellis, 2004; Ellis et al., 2003) often found among children growing up in socially and economically adverse family and neighborhood contexts.

Meaney and colleagues have employed the r–K heuristic to describe the alternative developmental pathways through which ecological conditions adaptively regulate the bio-

[5] An alternative perspective, proposed by Geary (2005), involves the evolution of adaptations that reduce ecological constraints on population growth (i.e., ecological dominance) and their relation to r- and K-selected strategies within species. According to this perspective, once a species gains ecological dominance, the primary selection pressures shift from external forces acting on a species to within-species competition for resources. Ecological dominance combined with migration into unexploited regions that impose little constraint on population growth favor r-based strategies, given high resource availability, low social competition, and low mortality. However, as resources decline, social competition will increase, which favors more competitive offspring and thus a shift to a more K-selected strategy.

behavioral development of offspring (see Fig. 4). At the level of maternal reproductive and stress physiology, variation in social and ecological contexts, along with individual differences in maternal physiology, biases mother–infant interactions toward one of two distinctive patterns of infant care, each with clearly definable behavioral markers. Under low stress conditions, mothers display a pattern of frequent licking and grooming (LG) of pups, along with a typical arched back nursing (ABN) posture. By contrast, under conditions of stress and adversity, mothers show much less frequent licking, grooming or arched back nursing of pups. In addition to such contextual influences on these care-giving behaviors, both patterns are also heritable and naturally occurring, and each pattern is typical of different strains of rodent. Female BALBc mice, for example, who display a predisposition to fearfulness and exaggerated HPA reactivity to stressors, characteristically evince low levels of LG–ABN (Anisman, Zaharia, Meaney, & Merali, 1998). On the other hand, C57 mothers, who show little behavioral evidence of fear and relatively low HPA reactivity, are those for whom high LG–ABN behaviors are typical. Heritable differences in maternal behavior appear to be highly stable from litter to litter (Champagne, Francis, Mar, & Meaney, 2003).

Although strain differences in maternal behavior exist, such differences can also be *induced*, by changes in the character of the natural or laboratory environment. First awareness of such plasticity in maternal behavior followed observations that the 'handling' of pups—regular, short-term mother-litter separations for the first few weeks of life—resulted in upregulation of LG–ABN behavior (Levine, 1994) and neurobiological changes closely aligned with those found in heritably less fearful animals (Meaney, 2001). As adults, animals handled in the postnatal period showed diminished fearfulness, dampened HPA reactivity to stressors, and decreased corticotrophin releasing hormone (CRH) mRNA expression in the paraventricular nucleus (PVN) and the central nucleus of the amygdala, both structures closely involved in the regulation of stress reactivity. Further, such diminution in behavioral and neuroendocrine reactivity to stressors is demonstrably mediated by an increase in the intensity and frequency of maternal LG–ABN in her post-reunion behavior with the pups, an alteration in mothering activity that directly calibrates the responsivity of the infant neural stress circuitry through changes in glucocorticoid receptor (GR) and CRH expression. In addition, postnatally handled female offspring show, as adults, increased numbers of estrogen receptors in the medial preoptic area (MPOA), increased lactation-induced, estrogen-mediated oxytocin expression, and upregulated oxytocin-facilitated dopamine release in the nucleus accumbens, a sequence of neural signals thought to regulate the onset and character of maternal behavior and the intensity of LG–ABN.

On the other hand, more prolonged mother-litter separations (e.g., 3 h per day over the first two weeks of postnatal life), produce biobehavioral changes in pups that are exactly opposite in character. Offspring sustaining long, stressful maternal separations show heightened fearfulness in novel conditions, upregulated HPA reactivity, and decreased lactation-induced oxytocin receptor expression. Such changes produce offspring with decreased GR expression, diminished feedback sensitivity, and thus increased CRH expression, high HPA reactivity and, among females, maternal behaviors that program similar reactivity in the subsequent generation.

Taken together, these observations indicate that heritable individual differences in mothering behavior and variation in maternal care-giving caused by ecological conditions in the natural environment—differences characterized by the level of LG–ABN

behavior—program experience-sensitive neural circuitry in the young, resulting in striking and enduring differences in offspring stress reactivity (see Fig. 4). Pups born into stable, supportive environments with only short-term stressors become predisposed, through high levels of maternal LG-ABN, to patterns of low stress reactivity and low levels of fearfulness. Pups born into conditions of longer-term and unpredictable stressors, on the other hand, become biased, through *low* maternal LG–ABN, toward fearfulness and heightened biological sensitivity to stressors. Even more remarkably, such individual differences in the first generation of offspring are transmitted into the second—a non-genomic intergenerational transmission—through perpetuated differences in maternal–infant behavior.

How are such consequences of maternal-infant interaction translated into adaptive variability in offspring behavior? The recent work of Weaver, Szyf and Meaney (Meaney & Szyf, 2005; Weaver et al., 2004) offers clear evidence for epigenetic regulation of stress responsive genes by maternal behavior. Epigenetic regulation refers to the modulation of gene expression through changes in the epigenome, that is, the chromatin structure and methylation of DNA. Low LG–ABN care by the mother causes developmental switches in the pups that lead to decreased GR expression through changes in DNA methylation at the GR gene promoter. Such differences in the epigenome emerged within the first week of life, could be reversed with cross-fostering to mothers with the opposite pattern of LG–ABN behavior, occurred only during this early sensitive period, and persisted into adult life. Changes in DNA methylation and histone acetylation (i.e., changes in DNA and its accompanying protein structures that physically regulate the accessibility of the gene by inhibiting the transcription factor binding required for DNA expression; see Robertson, 2005) are thought also to be responsible for the accompanying differences in NE production and GABA/BZ receptor binding in the amygdala found among pups raised by low and high LG–ABN mothers.

As outlined in Fig. 4, changes in the epigenetic regulation of genes guiding the development of central, stress-responsive circuits result in concomitant changes in offspring stress physiology and behavior (Cameron et al., 2005). Pups reared by low LG–ABN mothers in high stress environments show increased reactivity to stressors in both the HPA and sympathetic adrenomedullary axes, as well as enhanced vulnerability to stress-related forms of morbidity. Pups in high stress, low LG–ABN environments also demonstrate pervasively higher rates of fear-induced behavior, increased burying behavior in response to threats, stronger startle reflexes, and decreased open-field exploration. The biasing towards an r-selected life history strategy is most strikingly demonstrated by the reproductive development and behavior of the female offspring of low LG–ABN mothers. These pups experience earlier onset of puberty, are substantially more sexually proceptive toward novel males, exhibit increased lordosis in response to male mounts, have sharply higher rates of pregnancy following mating sessions (over 80%), and provide lower quality parental investment in their own offspring (low LG–ABN).

In contrast, pups reared by high LG–ABN mothers show relatively diminished HPA reactivity and startle responses, increased vulnerability to endotoxin-induced sepsis, but greater resistance to stress-induced illness. These physiologic differences are accompanied by behavioral differences, such as increased open field exploration and decreased latency to eat in novel environments. The biasing toward a K-selected life history strategy is manifest in the reproductive development and behavior of female pups that experience high LG–ABN maternal behavior. These pups experience later onset of puberty, tend to display

agonistic behavior in response to mounting solicitations by novel males, enforce much longer intervals between matings, have lower rates of pregnancy following mating sessions (50%), and provide higher quality parental investment in their own offspring (high LG–ABN).

The summarized work thus lays open a stepwise series of mechanisms—at varying levels of complexity and abstraction—by which ecological conditions can produce systematic differences in a rodent pup's experiences of maternal behavior, which throw regulatory switches that, in a developmental cascade, affect transcription of the pup's stress-responsive genetic material, the reactivity of its neural and neuroendocrine circuits, its timing of gonadarche, and its individual profile of defensive and reproductive behavior. In a seamless sequence of biological and behavioral processes, the developing pup's survival and reproductive strategies are adaptively calibrated to maternal resources and the frequency and duration of threats in the environment into which it was born.

A theory of adaptive phenotypic plasticity in the human stress response systems

Consistent with the work of Meaney and colleagues, Boyce and Ellis (2005) have articulated the precepts and rationale for a new claim about the nature of relations between early life experience and stress reactivity in humans, a claim that they have also explored empirically (Ellis, Essex, & Boyce, 2005). The logic of their argument can be summarized in the following way. Biological reactivity to psychological stressors consists of an elaborated, highly coordinated, but phylogenetically primitive set of neural and peripheral neuroendocrine responses, designed to ready the organism for external challenges and threats to survival. Standard explanations of such responses' role in the pathogenesis of human disorders suggest that prolonged or exaggerated reactivity, such as that seen in highly reactive biobehavioral phenotypes, exerts deleterious and impairing effects on a broad range of target organs, including structures within the brain, leading to decrements in health, cognition, and functional capacities. Often overlooked in such accounts is a body of anomalous observations, revealing oppositional, counter-regulatory processes within the stress response circuitry itself and, even more compellingly, bivalent effects of reactivity on biomedical and psychiatric outcomes. Highly reactive children sustain disproportionate rates of morbidity when raised in adverse environments but unusually low rates when raised in low stress, highly supportive settings (Boyce & Ellis, 2005).

Such bidirectional, environment-dependent health effects suggest that *biological sensitivity to context* is the core, defining feature of highly reactive phenotypes. These observations call into question the presumably unitary pathogenic effects of high reactivity and suggest that its protective effects within specific developmental ecologies might explain the conservation of such phenotypic variation over evolutionary history. Furthermore, adaptive phenotypic plasticity enables entrainment of biological and behavioral development to match early (and predicted future) social environments. Given past evidence that early trauma can evoke up-regulatory changes in stress reactivity and new evidence that high reactivity can be protective in highly supportive settings, Boyce and Ellis (2005) postulated a curvilinear, U-shaped relation, shown in Fig. 5, between levels of early adversity and the magnitude of biological response dispositions. Specifically, Boyce and Ellis hypothesized that: (a) exposure to acutely stressful childhood environments up-regulates stress reactivity, increasing the capacity and tendency of individuals to detect and respond to environmental dangers and threats; (b) exposure to exceptionally supportive childhood environments

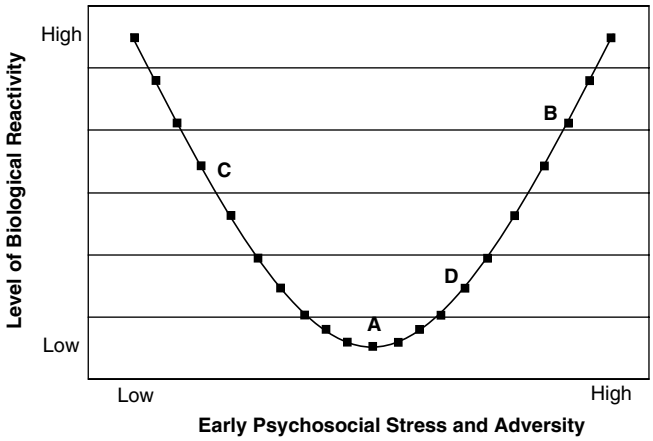


Fig. 5. Hypothesized curvilinear relation of biologic reactivity to early stress and adversity. Comparisons of subjects at points A and B would result in a conclusion that early adversity is associated with greater stress reactivity. Comparisons at points C and D, on the other hand, would generate the inference that early adversity produces diminished reactivity (from Boyce and Ellis, 2005).

also up-regulates stress reactivity, increasing susceptibility to the social and developmental benefits of such environments; and (c) typical of the large majority of children, exposure to childhood environments that are extreme in neither direction down-regulates stress reactivity, buffering individuals against the chronic stressors encountered in a world that is neither highly threatening nor universally safe.

Although the theory predicts up-regulation of stress response systems in both highly supportive and stressful environments (the U-shaped curve), high stress reactivity may translate into different behavioral phenotypes in supportive and stressful environments. Reactive, sensitive children have been found to be more reflective and perhaps more conscious of self and environment (Aron & Aron, 1997; Kagan, Snidman, Zentner, & Peterson, 1999; Lewis & Ramsay, 1997; Patterson & Newman, 1993), to be more able to delay gratification in pursuit of goals (Boyce, 2002; O'Hara & Boyce, 2001), and to perform better on neuropsychological measures of inhibitory control, executive function, and self-regulation (Blair, Granger, & Razza, 2005; Davis, Bruce, & Gunnar, 2002). The Boyce and Ellis (2005) model suggests that such abilities enable children to more fully absorb and take advantage of extant resources and opportunities in highly supportive environments. Thus, up-regulated stress response systems in children may interact with the protective, beneficial developmental environments to produce relatively high levels of cognitive and social competence. Conversely, interactions between high stress reactivity and risky, threatening developmental environments may result in lower thresholds for anticipating threat in ambiguous or unfamiliar situations (e.g., elevated sensitivity to threat-cues, such as angry faces) and support greater vigilance and wariness in children (see Gunnar, 1994).

This theorizing is consistent with primate research (Suomi, 1997), in which rhesus macaques were selectively bred for either high or average levels of stress reactivity and then cross-fostered to either highly skilled, nurturing mothers or to merely average mothers. The highly reactive infants fostered to nurturing mothers had the best developmental outcomes of the group (e.g., developmental precocity, behavioral resilience to psychosocial stressors, ascension within the group's dominance hierarchy), whereas the highly reactive

infants fostered to average mothers had the worst outcomes. Intermediate between these two extremes were the infants that were bred for average reactivity: their developmental outcomes differed little across the two mothering conditions. Remarkably similar results have derived from studies on genotypic variation in the serotonin transporter (5-HTT) gene-linked polymorphic region (5-HTTLPR) in interaction with experimental variation in early rearing experiences in macaques (Barr et al., 2003, 2004; Bennett et al., 2002).

Boyce and Ellis' (2005) curvilinear, U-shaped model of the development of stress reactivity has been initially investigated in two studies comprising 249 children and their families (Ellis et al., 2005). In the first study 3- to 5-year-old children were concurrently assessed on levels of support/adversity in home and preschool environments and on cardiovascular reactivity to laboratory challenges. In the second study children were prospectively assessed on familial stress in both infancy and preschool and on autonomic and adrenocortical reactivity to laboratory challenges at age 7. In both studies, a disproportionate number of children in supportive, low-stress environments displayed high autonomic reactivity. Conversely, in the second study a relatively high proportion of children in very stressful environments showed evidence of heightened sympathetic and adrenocortical reactivity. Consistent with the evolutionary-developmental theory, the exploratory analyses also generated the testable hypothesis that relations between levels of childhood support/adversity and the magnitude of stress reactivity are curvilinear, with children from moderately stressful environments displaying the lowest reactivity levels in both studies.

The evolutionary-developmental theory of Boyce and Ellis (2005) does not imply that children with highly reactive phenotypes have equal fitness, on average, with children whose reactivity profiles are in the low or normative range. Rather, the implication is that different reactivity profiles have different fitness costs and benefits in different environments. Boyce and Ellis (2005) contend that developmental switch mechanisms have been organized by natural selection to produce enhanced biological sensitivity to context when it is advantageous to the developing person—in both acutely stressful and exceptionally supportive childhood environments.

Gene–environment co-regulation of the stress response systems

The evidence reviewed in this paper suggests that adaptive individual differences in stress reactivity involves an integration of genetic influences and condition-sensitivity. This dual regulation needs to be explained at both a proximate and evolutionary level. At the proximate level, dual regulation fits readily into the West-Eberhard (2003) model. Indeed, genotypic and environmental effects on regulation are interchangeable in this model because the developing phenotype responds to them in much the same way. Specifically, impinging genotypic and environmental influences are integrated into a single threshold response at the level of the regulatory mechanism. It is the preexisting phenotype that defines the precise form of the response once the threshold has been passed. Consequently, the precise sources of influence on the regulatory mechanism, whether environmental or genetic, are of little consequence developmentally.

The same cannot be said at the evolutionary level of analysis. Evolutionary explanations focus on identifying and modeling the selection pressures that, over generations, have structured the regulatory mechanisms that control both the ratio and maintenance of alternative phenotypes in the population. Central to this adaptively structured control system is selective sensitivity to various forms of genetic and environmental information. Dual

genetic and environmental regulation of adaptive individual differences poses an evolutionary challenge because, as discussed in this paper, the selection pressures that favor genetic and environmental regulation are only partially overlapping. There are at least two ways to approach this issue. One rather extreme approach is to consider genotypic and environmental regulation as competing evolutionary models. In this scenario, one form of regulation will emerge empirically as the more successful account of adaptive trait variation and the other form of regulation will prove to be incidental (i.e., neutral or non-adaptive). Another way to conceptualize the evolution of dual regulation, however, is under the rubric of gene–environment interactions, in which different genotypes possess different norms of reaction. Recall that a norm of reaction represents the range of phenotypes that a given genotype can support under different environmental conditions. Accordingly, phenotypic plasticity—the developmental susceptibility of a trait to environmental influence—may vary across individuals as a function of genotype. That is, the influences of Genotype A on a specific trait may be more or less condition-dependent than the influences of Genotype B on that same trait (with trait plasticity itself subject to evolutionary change in the frequencies of Genotypes A and B). In humans, for example, a functional polymorphism in the promoter region of the serotonin transporter (5-HTT) gene moderates the influence of stressful life events on depression (Caspi et al., 2003; Eley et al., 2004; Grabe et al., 2004; Kaufman et al., 2004; Kendler, Kuhn, Vittum, Prescott, & Riley, 2005; cf. Gillespie, Whitfield, Williams, Heath, & Martin, 2005, who failed to replicate this finding). Specifically, individuals possessing 1 or 2 copies of the 5-HTT short allele have broader reaction norms for depression (i.e., they develop a broader range of depressive phenotypes in response to stressful life events) than do individuals who are homozygous for the long allele.

Consistent with the reaction norm perspective, Wilson (1994; Wilson and Yoshimura, 1994) has proposed an evolutionary model of the coexistence of adaptive genetic variation and adaptive phenotypic plasticity in multiniche environments. All else being equal, the presence of multiple niches in a single environment will favor developmental specialists (i.e., narrow genetic reaction norms in which phenotypic development is minimally condition-dependent) over developmental generalists (i.e., broad genetic reaction norms in which phenotypic development is highly condition-dependent) when individuals can evaluate and select niches that increase their fitness. This is because specialists outperform generalists in their preferred niche. However, multiniche environments are often characterized by negative density-dependence, meaning that as a given niche becomes more crowded (i.e., over-exploited relative to its size), the fitness benefits of specializing in that niche decrease. This is the cost of specialization. Indeed, as a given niche becomes overcrowded, more plastic individuals who can either developmentally entrain alternative strategies to exploit less saturated niches (polyphenism) or facultatively change strategies to exploit different niches over time (polyethism) gain a selective advantage. Given fluctuations in the size of niches over time and space, and corresponding fluctuations in the density of competitors in those niches, natural selection should favor a mix of developmental specialists (adaptive genetic variation) and developmental generalists (adaptive phenotypic plasticity) rather than a single genetic or environmental mode of regulation. In such fluctuating environments, specialists experience feast and famine while generalists experience intermediate outcomes (adjusting phenotypic development to exploit less crowded niches, but never doing as well in those niches as the specialists do). The generalists do not replace the specialists, therefore, but instead co-exist in stable equilibrium (Wilson, 1994; Wilson & Yoshimura, 1994).

Wilson's (1994) model of the coexistence of developmental specialists and generalists may have special relevance for understanding the evolution and development of alternative stress-response phenotypes. Several lines of evidence suggest that individuals who are high in stress reactivity are more phenotypically plastic; i.e., they more closely approximate developmental generalists who can match their phenotypes to prevailing conditions. In great tits, for example, Doves not only endure greater adrenocortical activation and body temperature changes in response to capture or social defeat than do Hawks, but they also appear to be more developmentally plastic and have a greater potential to achieve multiple or alternative phenotypes (Groothuis & Carere, 2005). Specifically, Doves are more aware of and responsive to external stimuli, are more likely to alter behavior patterns on the basis of experience, and deploy less consistent behavioral tactics over time than do Hawks (Groothuis & Carere, 2005). This enhanced responsivity to the environment has also been observed in human children who are biologically reactive to stress (Boyce & Ellis, 2005) and/or who display high negative emotional reactivity (Belsky, 2005). Indeed, an intriguing body of evidence in humans now points to links between levels of stress and support in childhood environments (e.g., quality of parenting, family stability and routines, SES) and indices of child health and behavioral adjustment that are reliably stronger among biologically reactive children (reviewed in Boyce & Ellis, 2005) and negatively emotionally reactive infants (reviewed in Belsky, 2005) than among their less reactive peers.

This increased susceptibility to rearing influence among reactive children suggests an important application of Wilson's (1994) model. On the one hand, in multiniche environments, natural selection should retain developmental specialists who are low in biobehavioral reactivity, whose traits and developmental trajectories have narrow reaction norms, and who achieve high fitness in the delimited social and ecological niches that match their genotype. On the other hand, in multiniche environments, selection should also retain developmental generalists who are high in biobehavioral reactivity, whose traits and developmental trajectories have broad reaction norms, who monitor childhood environments as a basis for entraining biobehavioral development to match local conditions, and who attain intermediate fitness outcomes across a range of niches (see especially Belsky, 2000, 2005). In this way, natural selection potentially maintains both adaptive genetic variation and phenotypic plasticity in the stress response systems.

Summary and conclusions

The theory and data reviewed herein strongly suggest that both the human nature and individual differences components of the stress response systems have been shaped and maintained by natural selection. We have conceptualized individuals differences as the products of adaptively structured, quantitatively variable, regulatory mechanisms that control patterns of gene expression involved in the development of alternative stress-response phenotypes. Calibration of these regulatory mechanisms—the setting of thresholds for conversion of phenotypes from one state to another, as well as the organism's ability to pass these thresholds—is co-determined by allelic variations and environmental factors. Alternative phenotypes are most likely to be maintained by natural selection in multiniche environments that afford different ways for individuals to survive and reproduce. Adaptively patterned variation maximizes disparities in survival and reproductive outcomes when all individuals are constrained to a single environment, but minimizes

these disparities when alternative phenotypes are allowed to inhabit (covary with) specialized physical and social environments in a multiniche system.

Genotypic regulation

Genotype-specific regulation means that one of several alleles that influence a switch mechanism predominates over others (and over environmental factors) in the magnitude of its effect and thus has a decisive impact on phenotypic determination. However, genotype-specific regulation that is immune to environmental influence is rare in nature. Genetic polymorphisms are most likely to be maintained by natural selection when advantages of niche specialization are high, when organisms can evaluate and select their niches, and when reliable environmental cues for entraining or switching between alternative phenotypes to match extant niches do not exist. Korte et al. (2005) proposed a model of adaptive genetic variation in alternative Hawk–Dove phenotypes. This model conceptualizes Hawk–Dove strategies as encompassing not only variation in behavioral phenotypes (e.g., bold-shy), but also underlying structural differences in neurobiology and systematic variation in the reactivity of the CRH and LC–NE systems. The model has been most extensively developed and tested in great tits. Covariation between Hawk–Dove strategies in great tits and fitness in fluctuating environments has provided an empirical basis for positing adaptive genetic variation. The core argument is that Hawks and Doves successfully inhabit different specialized niches that, as a result of stochastic variation in ecological conditions and density of competitors, fluctuate unpredictably across time and space. Over generations, therefore, allelic variations that contribute to individual differences in the development of alternative phenotypes along the Hawk–Dove continuum are maintained in equilibrium by natural selection. Although the Hawk–Dove model proposed by Korte et al. (2005) is not specific to human stress reactivity, it can serve as an evolutionary model for genetic variation in the human stress response systems[6].

To date, studies of genetic influences on Hawk–Dove strategies have focused almost entirely on partitioning variance components (i.e., deriving heritability estimates) rather than implicating any particular genes. A complete demonstration of adaptive genetic variation requires identification of relevant alleles, together with specification of the processes through which these alleles interact with environmental factors in development of alternative phenotypes. Because the regulatory mechanisms that control development of complex alternative phenotypes are influenced by multiple alleles (West-Eberhard, 2003), future molecular genetic studies could benefit from a polygenic approach. The multivariate regression techniques employed by Comings et al. (2000a, 2000b), which examine the relative influence of individual genes within a larger group of genes on externalizing disorders, provide an example of such an approach in humans.

[6] For a broad evolutionary model, such as the Hawk–Dove model presented by Korte et al. (2005), to remain plausible for a particular species, the model must be made specific to that species, such that the mode of regulation hypothesized and that observed in the species coincide. Hawk–Dove strategies represent alternative behavioral strategies for which many species appear homologous, making the model useful for understanding human genetic variation. However, for a strong argument to be made for adaptive genetic variation for Hawk–Dove strategies in humans, the selection pressures unique to humans must be modeled in a manner similar to that done in the great tits (*P. major*).

Environmental regulation

Adaptive phenotypic plasticity facilitates matching of the phenotype to the conditions where it is expressed. When the fitness of alternative phenotypes is predictable on the basis of reliable cues that have been recurrently present over evolutionarily time and can be detected and encoded by the individual, selection tends to favor adaptive phenotypic plasticity. This environmental regulation enables development of alternative phenotypes that promote fitness in variable environments. In the case of environment-specific regulation, one of several environmental cues that influence a switch mechanism predominates over others (and over allelic variations) in the magnitude of its effect and thus has a decisive impact on phenotypic development. Nonetheless, the concept of pure environment-specific regulation can be misleading. Even if phenotypic alternatives are primarily due to environmental effects, this does not mean that a population is genetically uniform in its propensity to adopt one phenotype over another.

A complete rodent model of adaptive phenotypic plasticity of the stress response systems and related behavioral and reproductive phenotypes has been developed by Michael Meaney and colleagues (e.g., Cameron et al., 2005). Based on life history theory, this model conceptualizes maternal behavior—licking, grooming, arched back nursing—as the prevailing mechanism through which ecological conditions are transduced to offspring. The rodent pup's experiences of maternal behavior throws regulatory switches that, in a developmental cascade, affect transcription of the pup's stress-responsive genetic material, the reactivity of its neural and neuroendocrine circuits, its timing of gonadarche, and its individual profile of defensive responses and reproductive behavior. In this manner the developing pup's survival and reproductive strategies are adaptively calibrated to the resources and threats of the environment into which it is born.

Consistent with Meaney's rodent model, Boyce and Ellis (2005) have developed a theory of adaptive phenotypic plasticity in the human stress response systems. This model reconceptualizes high stress reactivity as biological sensitivity to context, a response profile that may have increased survival and reproductive success in specific social and ecological niches that were recurrently encountered over human evolutionary history. Specifically, Boyce and Ellis hypothesize that biological sensitivity to context confers fitness benefits not only in highly stressful environments (by augmenting vigilance to threats and dangers), but also in highly protective environments (by increasing permeability to social resources and support). Ellis et al. (2005) report preliminary results that are consistent with this U-shaped hypothesis regarding conditional regulation of alternative stress-response phenotypes in humans. At the same time, much work is needed to fully test the model, including demonstration of within-person change in stress-response phenotypes under the environmental conditions specified by the theory, identification of alterations in chromatin structure and methylation of DNA that underpin these changes, links between alternative stress-response phenotypes and theoretically relevant patterns of behavior, and demonstration of enhanced fitness when specific stress-response phenotypes are matched to the environments that promote their development.

A central task in development of sophisticated human models of adaptive phenotypic plasticity is explication, based on theory and data from evolutionary biology, of evolutionarily relevant dimensions of childhood environments. Within species-typical boundaries, variation along these dimensions should systematically influence the regulatory mechanisms that control development of alternative stress-response phenotypes. Unfortunately,

human and non-human primate research has primarily examined the influence of pathological or species-atypical environments (e.g., severe abuse, isolate- or peer-rearing) on stress response systems (see reviews in Boyce & Ellis, 2005; Sanchez, Ladd, & Plotsky, 2001). Because natural selection adapts animals to environmental factors that were regularly encountered during their evolutionary history, comparisons between animals reared in species-typical and species-atypical environments are not, in and of themselves, sufficient for illuminating adaptive design. To fully understand an adaptive design, studies that involve assessment of the effects of different types of adversity that were regularly encountered in environments of evolutionary adaptedness are needed.

Along these lines, there may be qualitatively different classes of childhood stress that have divergent effects on the development of stress-response phenotypes and associated survival and reproductive strategies. For example, consider the work of Belsky (1999; Belsky et al., 1991) and Chisholm (1996; Chisholm et al., 2005) on the function of attachment styles. These authors conceptualize human attachment styles as phenotypic mechanisms that embody information about local environmental risk and uncertainty. Both Belsky (1999) and Chisholm (1996) posit that different types of insecure attachment embody information about distinct types of childhood stress (e.g., chronic adversity vs. unpredictability) and function to guide development of alternative survival and reproductive strategies that are matched to these distinct childhood contexts. Chisholm, Burbank, Coall, and Gemmiti (2005) have specifically linked this model to development of alternative stress-response phenotypes.

In conclusion, the evidence reviewed in this paper suggests that adaptive individual differences in stress reactivity involves an integration of genetic influences and condition-sensitivity, and that these genetic and environmental influences operate through adaptively structured regulatory mechanisms that control alternative developmental pathways. From an evolutionary-developmental perspective, two overarching questions concern (1) how this dual genetic-environmental regulatory system has been structured by natural selection and (2) what are the functions of the alternative stress-response phenotypes that emerge from this system? The central goal of this essay has been to provide an integrative, explanatory framework for addressing these questions.

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