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Human handedness and the concept of developmental stability

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Abstract

A model is proposed to explain the etiology of pathological handedness. Developmental instability, caused by elevated genotypic homozygosity, environmental disturbances, or their interaction, overrides programmed laterality and handedness in the same way that it perturbs the bilaterally symmetrical expression of morphological and metric traits. The model predicts that pathological handedness should be elevated among individuals with higher than average homozygosity and individuals who have developed under unfavorable uterine environments. Suggestions are offered for specific populations in which the predictions may be tested.

Introduction

Left hand preference, or sinistrality, is found in about ten percent of the population. Recent findings show that this direction and frequency of hand preference can be detected *in utero* by the end of the first trimester (Hepper *et al.*, 1990). Most researchers agree that hand preference has a hereditary component, but not all agree as to the genetic mechanisms involved (reviewed in Levy, 1977). Annett (1985) favors the role of a single gene with two alleles, the one for dextrality being dominant. Other researchers feel the hand preference results from a complex interaction of multiple genetic and nongenetic factors (Porac & Coren, 1981). While handedness is often dichotomized, it is more appropriately expressed as a continuum, because individuals who are right or left handed differ in the degree to which the nonpreferred hand is actually used in specific tasks (Annett, 1985). Thus, the literature contains terms like nonright-handed or mixed-handedness.

To complicate matters, an elevated incidence of nonright-handers has been repeatedly found in a number of different subpopulations. Significant departures from anticipated dextrality have been reported among individuals with a number of clinically defined phenotypes including autism (Soper *et al.*, 1986), schizophrenia (Green *et al.*, 1989), dyslexia (Annett, 1985) mental retardation (Soper *et al.*, 1987), low birth weight and prematurity (Searleman *et al.*, 1989), and immune disease Geschwind & Behan, 1982). Among nonclinically defined or normal subpopulations, handedness distributions have been reported to vary with factors like maternal age (Coren, 1990), life expectancy (Coren & Halpern, 1991) intellectual abilities (Kelshaw & Annett, 1983; Benbow, 1986), and even college major (Fry, 1990).

While the above references are relatively recent, an excess of nondextrality, especially among clinically defined sub-populations, has been noted and of interest for a long time, leading Satz (1973) to apply the term 'pathological left-handedness' to those individuals exhibiting left hand preference despite being genetically right-handed. The concept can be extended to right-handers as well, when dextrality is not expected based on family history. Use of the term 'pathological' in describing unanticipated shifts from right or left hand preference has some unfortunate connotations, but is now firmly entrenched in the literature. A model for the origin of pathological left-handedness was first described by Satz (1972) and developed more completely in subsequent contributions by Soper and Satz (1984), Porac and Coren (1981), Coren and Searleman (1990), and Coren and Halpern (1991).

In general, their model starts with 90% of the

population programmed to be right-handed and 10% left handed. Superimposed upon this, 10% of the entire population is caused by some unspecified pathological intervention to change from their programmed hand preference. Numerically, this means that 9% of the population shifts from right- to left-handedness while only 1% shifts in the other direction, resulting in an excess of nonright-handers. The exact nature of any pathological disturbance has not been unequivocally identified. Brain injuries before age six have been observed to shift hand preference (Satz, 1972), but this sort of trauma can only explain a small fraction of cases of handedness shifts.

A good deal of evidence has been gathered to support a strong association of birth related stressors with the shift in handedness (reviewed in Searleman *et al.*, 1989). However, complications at the time of delivery may, in many cases, reflect perturbations of earlier developmental events. These early interferences are compatible with the idea of a 'Rare Trait Marker' (Coren & Sealeman, 1990) and could be either of genetic or of nongenetic origin. Furthermore, not all individuals undergoing birth stress exhibit departures from anticipated handedness. Therefore, any model to explain pathological handedness must be able to account for its occurrence as well as its absence.

My purpose is not to discriminate among models proposed for the inheritance of handedness. However, there is a biological principle linking both population and developmental genetics that I think has value in explaining the etiology of what has become known as pathological left- (and right-) handedness. Below I describe the concept of developmental stability and offer a model in which genetic and/or environmental perturbations of developmental homeostasis can result in deviations from normal laterality patterns observed in certain subpopulations.

The concept of developmental stability

Developmental stability, or homeostasis, is the ability of an organism to develop according to its ontogenetic program despite adverse environmental conditions (Waddington, 1957). A variety of measures are typically employed in assessing developmental stability in animals. Major and minor physical anomalies (Waldrop *et al.*, 1971), sometimes known as 'phenodeviants' (Lerner, 1954), provide evidence of disruptive influences during development. The most widely used measure is called fluctuating asymmetry (FA), seen in paired bilateral traits (Palmer & Strobeck, 1986).

Fluctuating asymmetry, or FA, is only one kind of asymmetry seen in organisms with bilateral symmetry. In order to understand the biological significance of FA, it is helpful to first describe the other kinds of asymmetries observed in animals (Fig. 1). One of these is directional asymmetry (DA). In DA, all members of a species show consistent structural or functional bias for a particular side of the body.

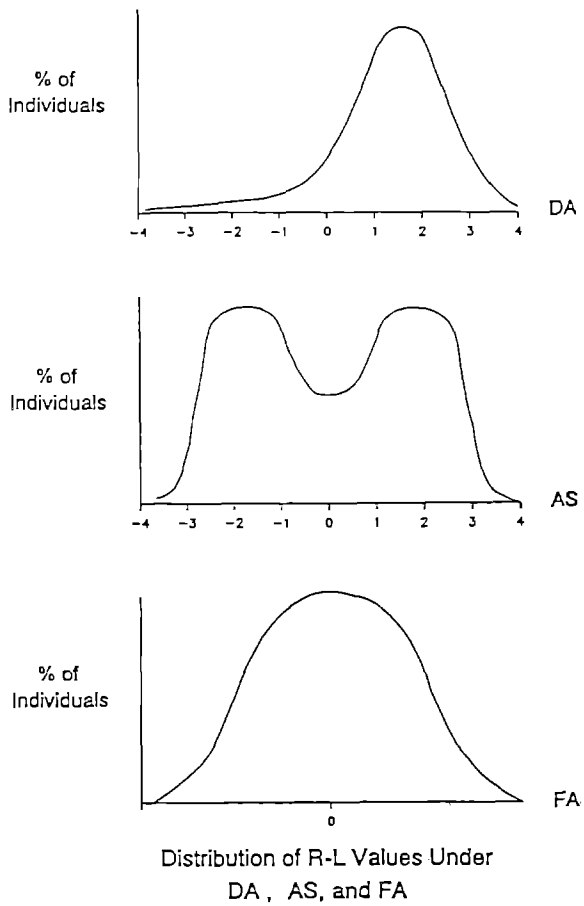

Fig. 1. Three different kinds of asymmetry found in bilaterally symmetrical organisms. DA or directional asymmetry is seen when the mean for the trait always exhibits the same right OR left bias for the species. In antisymmetry, or AS, there is always a bias for one side, but half of the population shows a bias for each side. Fluctuating asymmetry, FA, occurs when the distribution of right minus left values follows a normal curve.

Examples of DA include direction of shell coiling in snails, placement of the eyes in flatfish such as flounders, number of lobes in the right *vs.* left lung in humans, placement of the heart in humans, and localization of speech to the left hemisphere. Another kind of naturally occurring asymmetry is antisymmetry (AS). A trait showing antisymmetry is consistently exaggerated on one side of the body or the other, but within a population there is equal probability of it being on the right or left side. In male fiddler crabs, one claw is always greatly enlarged and is used in signalling. Because the enlargement occurs with equal frequency on either side, the trait exhibits the bimodal distribution typical of AS.

Fluctuating asymmetry (FA) also occurs randomly with respect to the right or left side but is produced when environmental factors interfere with the ability of an organism to execute its developmental plan equally on both sides. Fluctuating asymmetry is defined as the difference between the right and left sides for a trait, or the intrapair variance. In the absence of DA, it can be calculated by the formula R - L. Because the degree of developmental interference is variable in FA, it is distinguished from AS in that distributions of traits showing AS are bimodal or highly platykurtotic compared to the normal distributions of traits showing FA. Because for most bilateral traits the developmental program is the same for both sides, R - L should ideally be zero. However, because of developmental noise, this is not always the case. Levels of FA are used as a measure of the degree to which an organism can buffer itself against a wide range of environmental perturbations and still develop according to its genetically determined plan.

Origins of developmental stability and of fluctuating asymmetry

Two types of factors may influence developmental stability: genetic and nongenetic. Genetic influences on developmental homeostasis appear to be largely related to overall levels of the heterozygosity in the genome (Mitton & Grant, 1984). The relationship between high levels of heterozygosity and greater developmental stability is well known. Lerner (1954) discussed the repeated appearance of phenodeviants upon inbreeding or artificial selection in fowl, *Drosophila*, and mice. Fluctuating asymmetry has been shown to increase with laboratory schemes designed to reduce genetic variation (Leamy, 1984; Reeve, 1960; Today, 1955; Van Valen, 1962). A positive correlation between heterozygosity at allozyme loci and developmental stability has been reported in rainbow trout (Leary & Allendorf, 1989), marine bivalves (Mitton & Grant, 1984; Mitton & Koehn, 1985), *Poeciliopsis* (Vrijenhoek & Lerman, 1982; Quattro & Vrijenhoek, 1989) and man (Livshitz & Kobyliansky, 1985). The greater developmental homeostasis of highly heterozygous individuals is apparently due to the presence of more than a single molecular form of a gene product at a given locus, which results in an increased ability to compensate metabolically for a varying environment (Vrijenhoek & Lerman, 1982; Leary *et al.*, 1983, 1984).

Given the relationship between homozygosity and reduced developmental homeostasis, a prediction can be made about levels of FA in individuals who show extreme phenotypes for continuous traits with a polygenic basis. This prediction is generated from our understanding of multifactorial, polygenic traits shown in Figure 2. Examples of such continuous traits in humans include height, weight, IQ, and blood pressure. The additive genetic basis of continuous traits is described in genetics textbooks (Vogel & Motulsky, 1988). Continuous traits are primarily influenced by alleles at a large number of loci acting additively. For some traits, the role of one or more major effect loci has been detectable against a polygenic background (Thoday, 1961; Morton & MacLean, 1974; Lander & Botstein, 1987). For continuous traits, individuals whose phenotypes lie closer to the population mean tend to be more heterozygous at the responsible loci. Homozygosity can be seen to increase in extreme phenotypes. It follows that individuals with extreme phenotypes for continuous traits, being more homozygous, should also exhibit an increase in developmental instability. The prediction which follows from this relationship is that individuals whose phenotypes are in the tails of a distribution should tend to be more homozygous; thus, they should exhibit a higher degree of FA than individuals with average phenotypes (also shown in Fig. 2).

Evidence for physical manifestation of the homozygous condition has been repeatedly uncovered in humans: in dermatoglyphics (Soule & Couzin-

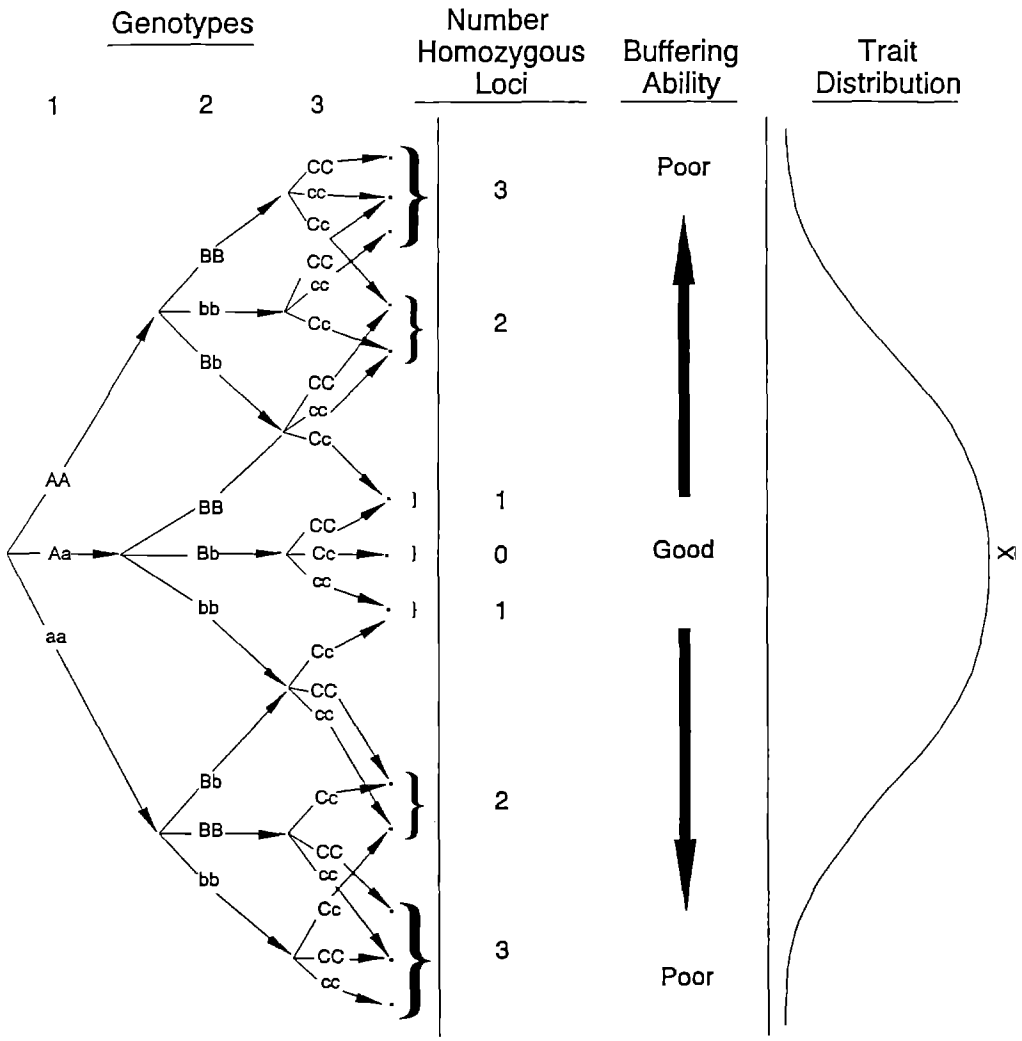

Fig. 2. The relationship between a quantitative trait with a continuous distribution, underlying genotypes, and the associated degree of developmental stability. Continuous traits with a normal distribution include birth weight, IQ, blood pressure, etc. Individuals near the population average tend to be more heterozygous than individuals in the tails of the distribution. (Modified from Lerner, 1954).

Roudy, 1982; Livshitz & Kobliansky, 1987; Markow & Martin, 1991), oral and facial clefts (Adams & Niswander, 1967; Woolf & Gianas, 1976, 1977), and numbers of teeth (Bailit *et al.*, 1970; Townsend & Brown, 1980; Smith *et al.*, 1983). For each of these physical traits, high levels of homozygosity are associated with an increased level of developmental instability as measured by FA.

The other important factor in developmental stability is the environment. Exposure to environmental stressors such as DDT concentration, mercury contamination, and low pH during development has been associated with increased FA in fish (Valentine & Soulé, 1973; Valentine *et al.*, 1973; Ames *et al.*, 1979). Audiogenic stress to mothers during gestation increases fluctuating dental asymmetry in rats (Siegel & Smookler, 1973). Other studies show evidence of the quality of the intrauterine environment on levels of FA in primates, including man. Advanced maternal age, poor maternal health, and even increased fluctuating asymmetry in the mother all have been reported to be associated with greater fluctuating asymmetry in offspring (Kohn & Bennett, 1986; Livshits & Kobyliansky, 1991).

Developmental stability, fluctuating asymmetry and pathological handedness

There is no reason to assume that the same developmental phenomena creating fluctuating asymmetry in bones, teeth, and hand prints would not also influence the developing CNS. Indeed, perturbations of normal symmetry/asymmetry patterns have been repeatedly found in studies of brain structure and function (reviewed in Markow, 1991). The CNS, by virtue of its existing hemispheric specializations, exhibits directional asymmetry, or DA. What would be the outcome of a situation causing developmental instability during the growth and differentiation of a lateralized or directionally asymmetrical organ system like the CNS? The possibilities include an enhancement of the programmed directionality, an elimination or reduction of any normal asymmetry, or a reversal of the programmed directionality. Because behaviors are the functional manifestation of normal lateralization patterns, behavioral changes are expected to accompany FA in the brain. When hand preference is the lateralized CNS trait of interest, the potential outcomes are presented in Figure 3.

Impaired developmental homeostasis will occur independently of, or superimposed upon, the genotype for handedness. The genetic mechanism for handedness is not important. Table 1 shows the relationship between genotypes and phenotypes for handedness. When an individual is programmed to be right-handed, in the absence of high levels of background homozygosity and/or stressful environmental conditions, he or she should develop

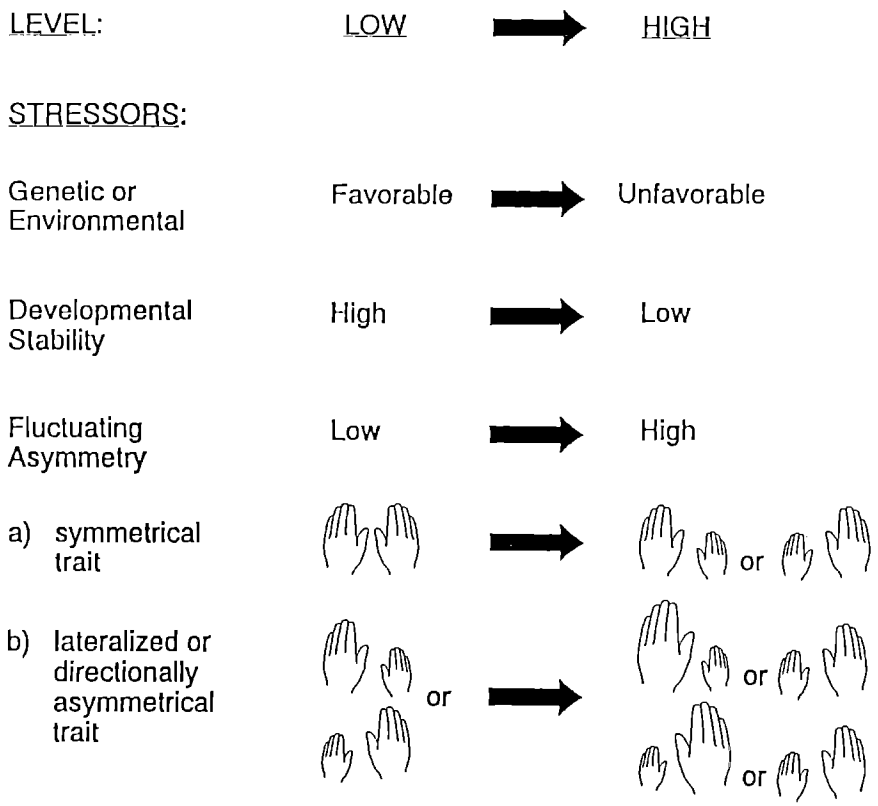

Fig. 3. Relationship between stressors, developmental stability and a trait such as hand preference. In this model, stressors contributing to reduced developmental stability are either homozygosity, poor environment, or both. For a trait that is normally symmetrical as depicted in a) where both hands are used equally, FAS will show up as an increase in preference for one hand over the other. In a given population there is equal probability of it being the right or left side. When the trait in question already exhibits some degree of directionality, such as right hand preference, developmental instability will reveal itself as either an exaggeration of the existing DA or some degree of reversal. The degree of reversal may be continuous such that some individuals may show only a slight reduction in their strength of hand preference while others may have either no preference or a reversal of programmed hand preference (pathological handedness).

Table 1. Interaction between handedness genotypes and fluctuating asymmetry for handedness phenotypes. The actual genetic basis for handedness is unimportant. Homozygosity levels referred to are at any loci in the genome.

Genotype for handedness	Relative homozygosity or environmental stress	Handedness phenotype
R	Low	RH
R	High	RRH + non RH
L	Low	LH
L	High	LLH + non LH

according to plan and be right-handed. However, should some aspect of his or her genotype or environment compromise developmental homeostasis, fluctuating asymmetry is increased and may manifest itself in some degree of nondextrality, mixed handedness, or hyperdextrality. The latter would be more difficult to detect in the largely right-handed population unless assessed via tests with the necessary sensitivity (see Annett, 1985). Developmental homeostasis could be perturbed as early as the first trimester, or later during delivery. While labor and delivery records usually make it easiest to pinpoint specific birth complications, earlier insults also leave their mark as well in the form of FA in developing morphological traits.

Predictions from this model are already partially testable from a review of the literature. One prediction is that individuals whose phenotypes for a continuously distributed polygenic trait are significantly higher or lower than the population average should be characterized by an excess in departures from anticipated handedness. An increase in nondextrality among the mentally retarded (Hardyck, 1977; Soper *et al.*, 1987) as well as among the academically gifted (Hardyck, 1977; Annett, 1985; Benbow, 1986) supports this prediction. While the relationship between low birth-weight and nondextrality (Searleman *et al.*, 1989) is also predicted by the model, hand preference of high birth-weight individuals remains to be directly examined. One could infer from the relationship between delivery complications and nondextrality that larger babies (thus those with labor and delivery difficulties) do in fact show hand preference deviations, but a more direct test is necessary. Vulnerability to schizophrenia appears to have a multifactorial threshold basis (Gottesman, 1991) in which affected individuals are predicted to have greater homozygosity at multiple genetic loci and hence greater fluctuating asymmetry. These predictions are supported by studies of brain imaging and dermatoglyphics (Markow, 1991) as well as by increased non-dextrality (Green *et al.*, 1989; Lishman & McMeekan, 1976; Taylor *et al.*, 1982) among schizophrenic subjects.

Other stressors should also be associated with pathological handedness. Birth stress has been most consistently shown to be associated with altered lateral preference (Searleman *et al.*, 1989), but as pointed out above may be related to infant size. However, Searleman *et al.*, (1988) and Livshits *et al.*, (1988) have shown that maternal laterality patterns or maternal developmental stability may themselves promote nondextrality or developmental instability in children.

The model in which developmental homeostasis influences laterality also makes predictions for species in which hand or paw preference exists but is non-directional. This would include those species, like the house mouse, in which animals may preferentially use one side, but for any given individual there is an equal probability that it will be the right or the left. Those mice who are relatively homozygous would exhibit greater developmental instability, greater FA, and would be expected to show stronger sidedness as a manifestation of that FA (Fig. 2). This is exactly what is seen in strains of mice either inbred or selectively bred for paw preference over a number of generations (Collins, 1977). The average degree of sidedness increases as the strains become more homozygous, but without any directionality in the population.

Finally, the aforementioned model bears directly on the action of balancing or stabilizing selection in human populations. Balancing selection is defined as reduced fitness of extreme phenotypes. When dealing with a simple situation such as a single locus with two alleles, balancing selection favors the heterozygote. When dealing with a continuous trait having an additive genetic basis, individuals in the phenotypic extremes or with rare traits (Coren & Searleman, 1990) show reduced fitness. The most widely cited example of stabilizing selection in man is birth weight (Karn & Penrose, 1952): infants with either high or low birth weights show

reduced survival. Interestingly, individuals who are extreme in their sinistrality to dextrality appear to exhibit disadvantages on a number of intellectual measures, leading Annett (1985) and Annett and Manning (1989) to suggest balancing selection acting on hand preference. If some cases of extreme or reversed hand preference reflect FA as a function of reduced developmental stability, then reduced performance by these individuals will reflect balancing selection on a larger portion of the genotype than just the gene or genes for handedness.

An attractive feature of the concept of developmental stability is that the responsible factors may be genetic and/or nongenetic and may affect the phenotype at different times along the developmental continuum. Early developmental perturbations may exert a more general influence on developing structures and ultimately their function. Stresses occurring later, such as at the time of delivery, will act on structures that had developed normally until that time. Furthermore, certain genotypes will be better able to buffer developmental insults than others. Thus, genetic and environmental variability can interact in a large number of ways to create the often perplexing variability observed in human laterality phenotypes.

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