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Individual differences in developmental plasticity: A role for early androgens?

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ABSTRACT

Developmental plasticity is a widespread property of living organisms, but different individuals in the same species can vary greatly in how susceptible they are to environmental influences. In humans, research has sought to link variation in plasticity to physiological traits such as stress reactivity, exposure to prenatal stress-related hormones such as cortisol, and specific genes involved in major neurobiological pathways. However, the determinants of individual differences in plasticity are still poorly understood. Here we present the novel hypothesis that, in both sexes, higher exposure to androgens during prenatal and early postnatal life should lead to increased plasticity in traits that display greater male variability (i.e., a majority of physical and behavioral traits). First, we review evidence of greater phenotypic variation and higher susceptibility to environmental factors in males; we then consider evolutionary models that explain greater male variability and plasticity as a result of sexual selection. These empirical and theoretical strands converge on the hypothesis that androgens may promote developmental plasticity, at least for traits that show greater male variability. We discuss a number of potential mechanisms that may mediate this effect (including upregulation of neural plasticity), and address the question of whether androgen-induced plasticity is likely to be adaptive or maladaptive. We conclude by offering suggestions for future studies in this area, and considering some research designs that could be used to empirically test our hypothesis.

1. Introduction

Plasticity can be defined as the ability of an individual organism to express a range of phenotypes under different environmental conditions. Phenotypic adjustments may take place on various timescales, from real-time shifts in physiology and behavior to stable, long-lasting patterns of trait expression in response to the individual's early environment (Kuzawa and Thayer, 2011; Snell-Rood, 2013). The latter kind of response is usually described as *developmental plasticity* (Schlichting and Pigliucci, 1998; West-Eberhard, 2003). While developmental plasticity is widespread in nature and can be highly beneficial, individuals within a species may differ widely in their ability to respond to the environment by developing alternative phenotypes (e.g., Dingemanse et al., 2012; Dingemanse and Wolf, 2013). The flip side of plasticity is *canalization*—the ability to buffer developmental processes against genetic and environmental perturbations (Debat and David, 2001); canalization allows organisms to achieve consistent levels of trait expression despite variable conditions. Variation in plasticity can originate from genotypic differences, but also from early environmental factors such as prenatal hormones that modulate an individual's susceptibility to later contextual effects (Belsky and Pluess, 2013; Del Giudice, 2015a; Ellis et al., 2011).

Plasticity *per se* is not necessarily adaptive, and there are multiple hypotheses about the evolution of individual differences in developmental plasticity. An especially interesting case is that of *differential susceptibility*, a pattern whereby the same factors that increase plasticity in response to poor or harsh conditions (for example by prompting the development of high aggression and impulsivity in dangerous, unpredictable contexts) also amplify plastic responses to favorable conditions (e.g., low aggression and impulsivity in safe contexts; Belsky,

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1997, 2005; Belsky et al., 2007; Belsky and Pluess, 2009, 2013; Boyce and Ellis, 2005; Ellis et al., 2011). From an evolutionary standpoint, differential susceptibility may evolve as a form of "bet-hedging" or insurance against unpredictable environmental changes, but also as a way to better match the individual's phenotype to future conditions—particularly when plasticity itself is partly determined by early cues such as prenatal stress or adversity in infancy (Belsky, 1997; Boyce and Ellis, 2005; Del Giudice, 2015a; Frankenhuis et al., 2016). Adaptive plasticity is not limited to cues about the external environment, and may also evolve to match phenotypic development to indicators of an individual's condition (e.g., early cues of stress-induced damage that predict increased mortality in the future; see Nettle et al., 2013; Rickard et al., 2014).

Studies of differential susceptibility in humans have mainly focused on genetic variation and genotype-environment interactions, with an emphasis on candidate genes in serotonergic and dopaminergic pathways (see Belsky and Pluess, 2009; Del Giudice, 2017a; Ellis et al., 2011; Moore and Depue, 2016; van Ijzendoorn and Bakermans-Kranenburg, 2015). Other research has investigated phenotypic traits that may modulate individual plasticity, such as early temperament and stress physiology (e.g., Belsky, 2005; Ellis et al., 2005; Feurer et al., 2017; Slagt et al., 2016). These traits develop under the joint influence of genetic and environmental factors, and their effects on plasticity manifest as systematic patterns of phenotype-environment interactions (Belsky and Pluess, 2013; Del Giudice, 2016). Despite some preliminary evidence that prenatal exposure to stress-related hormones such as cortisol may increase susceptibility to postnatal experiences (Bosquet Enlow et al., 2017; Pluess and Belsky, 2011), we still know very little about the physiological factors that determine individual differences in plasticity.

Here we advance the novel hypothesis that androgen exposure during prenatal/early postnatal life (and possibly at later developmental stages) modulates developmental plasticity in humans. Specifically, we suggest that: (a) higher male variability across phenotypic traits is partly explained by higher plasticity in males as a group, which in turn is influenced by early androgen exposure; and (b) for traits in which males are more variable than females, higher levels of early androgens should increase *individual* susceptibility to the environment in both sexes, above and beyond their directional effects on development (e.g., behavioral masculinization; Hines, 2011). Since a majority of physical and behavioral traits show greater male variability (see below), the net effect of androgens across multiple traits and environmental variables should be plasticity-enhancing. While this hypothesis is speculative, it is consistent with evolutionary models of sexual selection and multiple lines of evidence from human and non-human studies, as we discuss in detail below. If our hypothesis gains empirical support, the current focus on stress hormones and central neurotransmitters as key contributors to plasticity (e.g., Moore and Depue, 2016) will have to be widened to include sex hormones and associated neurobiological pathways, opening up a potentially fruitful avenue for developmental research.

The paper is organized as follows. We begin by reviewing evidence that human males are more phenotypically variable than females in a broad range of traits, and that developmental plasticity likely contributes to greater male variation. We also discuss evolutionary models of why selection leads to sex differences in variability across species, and review empirical results that document increased susceptibility to the environment in males. These empirical and theoretical strands converge on the hypothesis that androgens may promote developmental plasticity for traits that show greater male variability. (While the plasticity-enhancing effects of androgen might extend to other traits, the logic of the hypothesis applies most clearly to those in which males are more variable than females.) We consider a number of potential mechanisms that might mediate this effect, including—but not limited to—androgen-dependent upregulation of neural plasticity, and discuss the question of whether androgen-induced plasticity is likely to be adaptive or maladaptive. We conclude with suggestions for future research on this topic.

2. Sex differences in variability

In humans, it is well documented that a majority of phenotypic traits are more variable in males than in females (Lehre et al., 2009). To begin, higher male variance is found in anatomical features such as adult height and body mass, birth weight, and facial morphology (Claes et al., 2012; Holloway, 1980; Lehre et al., 2009; Lippa, 2009). The same pattern is apparent in brain anatomy: starting from infancy, males show a wider range of volume, both in the brain as a whole and in several specific regions (Ritchie et al., 2017; Wierenga et al., 2017).

For traits such as height and brain size, sex differences in variance correlate with sex differences in means—e.g., men are taller on average *and* show higher variance in height. The coefficient of variation (mean divided by standard deviation) of height, body mass, and brain volume is similar in men and women, suggesting that sex differences in variance are partly or largely due to scaling effects (Holloway, 1980; Lippa, 2009; Miller and Penke, 2007). However, males also show greater variability in traits in which average differences are negligible or favor females. An important example is general intelligence, as measured for example by IQ tests. General intelligence is significantly more variable in men, but the average difference between the sexes is close to zero. As a result, men end up being over-represented at both the high *and* low end of the intelligence distribution; the same pattern is found in measures of academic performance (e.g., Arden and Plomin, 2006; Johnson et al., 2008; Lehre et al., 2009). Sex differences in personality provide further evidence. On average, women have similar or higher scores than men on the dimensions of personality known as the "Big Five"—*extraversion*, *conscientiousness*, *agreeableness*, *openness to experience*, and *neuroticism* (emotional instability). And yet, when personality is rated by external observers men are more variable in most of these traits, with the exception of neuroticism (Borkenau et al., 2013a,b; see Del Giudice, 2015b). Other behavioral phenotypes showing higher male variability include physical aggression, preferences for uncommitted sex with casual partners versus committed relationships with stable partners (*sociosexuality*), creativity, autistic-like symptoms, and even left/right handedness (see Archer and Mehdikhani, 2003; Del Giudice et al., 2010, 2014; He and Wong, 2011; Karwowski et al., 2016; Lippa, 2009, 2010; Papadatou-Pastou et al., 2008; Ruzich et al., 2015; Schmitt, 2005; Schmitt et al., 2003).

In principle, sex differences in variability could reflect magnified expression of genetic factors in males, with the same amount of environmentally induced variance in the two sexes. If this were the case, *heritability* (the proportion of phenotypic variance explained by genotypic differences among individuals) should be higher in males, at least for traits that show excess male variability. However, a recent large-scale meta-analysis revealed that the narrow-sense (i.e., additive) heritability of physical, behavioral, and physiological traits (including personality and intelligence) estimated from twin studies does not differ systematically between the sexes; nor is there evidence that non-additive genetic factors play a larger role in males (Polderman et al., 2015). In fact, a recent genomic study (in which heritability was estimated from common alleles) found higher heritability in females for a number of traits including body size, hair and skin color, blood pressure/hypertension, and diabetes risk (Ge et al., 2017). (One possible interpretation of this finding is that *de novo* mutations and rare variants in an individual's genome—which are not included in genetic scores based on common alleles—tend to have larger phenotypic effects in males than in females.)

The combination of higher trait variance and equal (or even lower) heritability indicates that the excess phenotypic variance of males is not entirely genetic in origin, and could be partly accounted for by stronger *environmental* effects. Furthermore, twin studies consistently show that environmental effects for most traits are largely *nonshared*—that is, they