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,

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 nonhuman 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

act independently on siblings within the same family and do not make them more similar to one another. For cognitive and personality traits, the relative contribution of nonshared effects increases with age and accounts for the near-totality of the environmental variance in adulthood (Knopik et al., 2017; Polderman et al., 2015). The fact that environmental effects on behavioral traits are mainly nonshared is important because models of differential susceptibility imply the existence of systematic genotype- and phenotype-environment interactions, whereby similar conditions elicit different responses in different individuals (Belsky and Pluess, 2009; Belsky et al., 2007; Ellis et al., 2011). In classical twin studies, such interactions increase the size of estimated genetic and/or nonshared environmental effects, but not that of shared effects (see Del Giudice, 2016; Duncan et al., 2014). Of course, a possible alternative is that males are more affected by random developmental noise, which also contributes to inflate the nonshared environmental variance.

As it turns out, the pattern just described is by no means unique to humans. In the majority of sexually reproducing species, males show higher variability than females in a broad range of phenotypic traits, especially (but not only) those directly related to reproduction and mating. Importantly, the robust difference in phenotypic variability observed across species is not primarily explained by sex differences in additive genetic variation, which tend to be small and inconsistent like those in trait heritability. Instead, sex differences are mainly found in the remaining portion of the variance, which captures both environmental and nonadditive genetic effects (Wyman and Rowe, 2014). One meta-analysis found evidence that males are more variable than females in species in which they are the heterogametic sex, presumably as a consequence of carrying two different chromosomes (e.g., XY in humans; Reinhold and Engqvist, 2013). However, a second comparative meta-analysis failed to support this particular hypothesis (Wyman and Rowe, 2014). Whatever the contribution of sex chromosomes, higher variability in males is unlikely to be a simple byproduct of heterogamy, and more likely to reflect a history of specific selective pressures, as we discuss next.

2.1. Evolutionary models of sex differences in variability

Although they differ in the specifics, most evolutionary models converge on sexual selection as the most plausible explanation for sex differences in variability (e.g., Geary, 2015; Hill and Tabachnikov, 2017; Pomiankowski and Møller, 1995; Rowe and Houle, 1996). In the majority of animal species, males undergo stronger sexual selection through (inter-sexual) choice by females and (intra-sexual) competition with other males. As a consequence, they are typically selected to express more extreme versions of traits such as ornaments, weapons, and quality signals. Sexually selected traits are comparatively less canalized, and are especially vulnerable to harmful mutations, environmental stressors, and other developmental perturbations (e.g., early life infections, poor nutrition). The heightened condition dependence of sexually selected phenotypes should contribute to increase both genetic and environmental variance in males (Geary, 2015, 2016, 2017; Pomiankowski and Møller, 1995; Rowe and Houle, 1996).

Males are also considerably more likely to show a range of alternative reproductive strategies (or "tactics" in the usage of some authors), which may be optimal under different circumstances and environmental conditions (Engqvist and Taborsky, 2016; Taborsky and Brockmann, 2010). For example, some males may develop phenotypes specialized for aggressive competition and mating with multiple females, whereas others may engage in greater parental investment and provisioning (for a discussion of alternative reproductive strategies in men, see Bribiescas et al., 2012). In environments that fluctuate unpredictably, random variation in alternative mating/reproductive strategies could be adaptive as bet-hedging and increase phenotypic variance in males (Archer and Mehdikhani, 2003; Miller, 1997, 2001). Note that the relative importance of bet-hedging in organisms with long

lives and high parental investment—such as humans—has not been conclusively established. However, the same general argument is consistent with the idea that mating/reproductive strategies are developmentally plastic, and partly calibrated by early cues about the characteristics of the environment and/or the individual's competitive ability (e.g., nutrition, physical strength; Belsky et al., 1991; Bribiescas et al., 2012; Engqvist and Taborsky, 2016; Gettler et al., 2015; Kuzawa et al., 2010). Indeed, adaptive developmental plasticity and bet-hedging can easily coexist in the same organism, and may even depend on the same physiological mechanisms (see Donaldson-Matasci et al., 2013; Sadeh et al., 2009).

To summarize, evolutionary models suggest two distinct explanations for greater male variability. On the one hand, males show a wider range of mating/reproductive strategies (whose development may partly depend on contextual cues received in early development); on the other hand, males are expected to show stronger condition dependence in many sexually selected traits. In both cases, females stand to benefit less from phenotypic diversification, and may pay more severe fitness costs for deviations from average trait values. The two explanations are not mutually exclusive, but they have somewhat different implications for the nature of individual differences. Models of alternative strategies view individual differences as generally adaptive variants that can be optimal in different contexts. In contrast, models of condition sensitivity view phenotypic variation as largely due to differences in genetic and environmental quality (e.g., individuals who suffer from poor nutrition may become physically smaller or less aggressive). Importantly, different explanations may apply to different traits; for example, deleterious mutations seem to play a much larger role in the development of intelligence than in that of personality (Hill et al., 2017; Penke and Jokela, 2016).

3. Sex differences in developmental plasticity

The idea that males are more susceptible to environmental effects than females has a long history in anthropology (e.g., Greulich, 1951). On average, prenatal and childhood stressors of various sorts influence the growth of boys more strongly than that of girls; conversely, there is evidence that males respond more to positive interventions such as nutritional supplementations during gestation (Aiken and Ozanne, 2013; Martel, 2013; Stinson, 1985; Thayer et al., 2012). Girls who suffer from early undernutrition tend to show more rapid catch-up growth than boys, an effect that has been interpreted as reflecting stronger canalization of physical development (Stinson, 1985). Likewise, populations that undergo nutritional stress tend to show reduced sexual dimorphism in height, which indicates a disproportionate effect of nutrition on male growth (Gray and Wolfe 1980; Schmitt, 2015).

More generally, prenatal and early postnatal growth has been found to predict a range of adult outcomes including health, body size, body composition (e.g., muscularity), and behavior (e.g., number of sexual partners); these predictive relations tend to be consistently stronger in males than in females (e.g., Kuzawa, 2007; Kuzawa and Adair, 2003; Kuzawa et al., 2010). Patterns of higher male plasticity are not limited to the effects of early stress and nutrition: for example, although the underlying pathways are no doubt complex, education and psychosocial interventions typically have stronger positive effects on the long-term health of boys compared with that of girls (Conti and Heckman, 2010; Conti et al., 2016). In the literature on differential susceptibility to parenting quality and psychosocial interventions, a number of studies have reported significant genotype-environment interactions in boys, but not in girls (e.g., Belsky and Beaver, 2011; Chhangur et al., 2017). Of note, other studies have found stronger environmental effects in girls (e.g., Laceulle et al., 2014), so the available evidence is not unequivocal.

Classically, findings of higher male plasticity have been explained as manifestations of stronger developmental buffering in females, with the function of preserving adult reproductive functioning in the face of

perturbations (Stinson, 1985). This account emphasizes the adaptive benefits of canalization; conversely, the sexual selection models discussed in the previous section stress that decanalization and condition sensitivity can also be adaptive when traits serve signaling and competitive functions, which is more often the case in males (Geary, 2015, 2016). A third and not inconsistent possibility is that male reproductive strategies are both more variable *and* more plastic. If so, males would be expected to be more sensitive to early cues about the relevant features of the environment and/or traits that indicate their own survival prospects and competitive ability (Bribiescas et al., 2012; Kuzawa, 2007; Kuzawa et al., 2010).

Note that these evolutionary arguments do not imply that females are *always* less susceptible to environmental factors than males. On the contrary, females should be particularly responsive to those aspects of the environment that specifically impact their reproductive strategies. For example, early family stress appears to accelerate the timing of puberty in girls but not in boys, at least in the nutritionally rich environment of Western societies (see Belsky, 2012; James and Ellis, 2013). Starting from adolescence, girls are also more sensitive to the effects of close relationships on the risk for depression, consistent with the fact that female reproductive success is more strongly tied to the quality of social support networks (Martel, 2013). Girls also respond somewhat better than boys to interventions designed to prevent the onset of depression (Stice et al., 2009). In turn, depression risk is strongly predicted by neuroticism (Barlow et al., 2014), which is the only major dimension of personality to show greater variability in women.

The nonhuman literature on sex differences in developmental plasticity is harder to interpret with confidence, partly because of the small sample size of most studies. There are data indicating that both early stress and early enrichment affect male rats more than female rats (e.g., Bhatnagar et al., 2005; Elliott and Grunberg, 2005; Mueller and Bale, 2008; Peña et al., 2006) however, the literature as a whole is somewhat contradictory (Aiken and Ozanne, 2013), and possibly confounded by sex-specific effects of factors such as prenatal stress and nutrition (Glover and Hill, 2012). More generally, it is uncertain how relevant findings in these species are for understanding the nature and evolutionary origins of human sex differences in plasticity, given the marked inter-species differences in lifespan and reproductive strategies.

4. Androgens and plasticity

In the previous sections we reviewed evidence that, in our species, males are not just more variable on a wide range of phenotypes—including some traits in which average sex differences are negligible or favor females—but also appear to be more susceptible to a variety of environmental factors, both positive and negative. Of course, these statements are not meant as absolutes; exceptions include higher female variability in some traits (e.g., neuroticism; Del Giudice, 2015b) and female-specific sensitivity to some aspects of the early environment (see Glover and Hill, 2012; Martel, 2013). Likewise, sexual selection models suggest that condition sensitivity may be higher in females for traits that are specifically involved in female courtship or intrasexual competition (Geary, 2015).

A number of scholars have highlighted the likely role of early androgens in the development of sexually differentiated developmental trajectories (e.g., Aiken and Ozanne, 2013; Kuzawa et al., 2010; Miller, 2001). Some have even proposed that the prenatal surge of testosterone marks a sex-specific window of plasticity in male fetuses (Martel, 2013). However, previous work in this area has focused mainly on the *directional* effects of androgens (e.g., increased muscularity, higher aggression and risk-taking). Here we take this idea one step further and hypothesize that androgens may contribute to both sex *and* individual differences in developmental plasticity. The logic of this hypothesis applies most clearly to traits in which males are more variable than females, since greater male variance suggests a link between androgen

exposure and increased sensitivity to the environment. If our hypothesis is correct, being exposed to higher levels of androgens during early development should lead to increased susceptibility to the environment for a number of traits, either concurrently (e.g., prenatal stress, early infections) or prospectively (e.g., nutritional and social stressors in childhood). In turn, androgen exposure reflects the interplay of multiple genetic and environmental factors (e.g., individual differences in androgen synthesis, maternal levels of androgens during gestation), and is itself partly heritable (e.g., Caramaschi et al., 2012; Hoekstra et al., 2006; Paul et al., 2006).

It may be useful to note that our argument is not circular or tautological. We are not simply stating that males are more variable than females in some traits, and that sex differences in variability must be explained by sex differences in androgen exposure. We are making two additional, novel, and falsifiable claims: first, that androgens increase variability by amplifying *plasticity* to environmental factors (at least in part); and second, that differences in androgen exposure contribute to *individual* differences in plasticity in addition to sex differences.

Importantly, there is no reason to believe that androgens influence plasticity only in males. According to our hypothesis, differential exposure to early androgens should modulate plasticity in both sexes—even if the effect could be stronger in males owing to sex differences in dosage, interactions with other hormones, or other sex-specific effects. In other words, early androgens may make a larger contribution to environmental susceptibility in males because of their higher concentrations during early development, whereas other factors may play a comparatively more prominent role in females.

This idea is compatible with recent research that might, on the surface, be interpreted as running counter to our hypothesis, such as the widely circulated study by Sharp et al. (2015). These investigators found that maternal anxiety (used as a proxy for prenatal exposure to stress hormones) made girls—but not boys—more susceptible to the beneficial effects of postnatal stroking on later anxious/depressive symptoms. Note that this study did not find greater plasticity in females; what the results indicate (if replicated) is that prenatal stress has a stronger influence on postnatal plasticity in females compared with males. Moreover, anxiety and depression are correlates of neuroticism, the only broad personality traits that is systematically more variable in females than in males. In the context of our hypothesis, this finding is compatible with the idea that, in females, the effects of prenatal stress hormones overshadow those of androgens, particularly for traits with greater female variability (see also Zijlmans et al., 2015). The interplay between multiple endocrine systems can become quite complex; for example, it is possible that prenatal cortisol has stronger plasticity-enhancing effects in females, but stronger *directional* effects in males owing to its interaction with androgens (see e.g., Lee et al., 2014; Thayer et al., 2012).

Another key question is whether androgens are likely to promote plasticity only during the initial phase of development (i.e., prenatal and early postnatal exposure) or whether exposure later in life—for example in middle childhood and adolescence—may increase susceptibility as well. All else being equal, plasticity across species tends to peak early in life (see Fawcett and Frankenhuis, 2015; Fischer et al., 2014); however, long-lived organisms like humans may evolve multiple sensitive windows or developmental "switch points" (West-Eberhard, 2003). Even in rodents, there is evidence that puberty can be a window of plasticity for social behavior (Meyer et al., 2016; Zimmermann et al., 2017).

Evolutionary-developmental psychologists have argued that human reproductive strategies do not develop solely based on the cues received in the first years of life, but involve multiple transitions during which new aspects of the environment (e.g., feedback from peers, mating success) become salient and are integrated with previous information (Del Giudice and Belsky, 2011; Ellis, 2013). One of the key transitions in physical and behavioral development occurs between early and middle childhood. Perhaps not coincidentally, this transition is marked

by the secretion of increasing amounts of androgens by the adrenal gland (*adrenarche*), in girls as well as boys. These hormones—mainly dehydroepiandrosterone (DHEA) and its sulfate (DHEAS)—can be converted to testosterone and estrogen in various organs, including the brain (see Campbell, 2006, 2011; Del Giudice, 2014; Del Giudice et al., 2009). For all these reasons, we predict that prenatal and early post-natal androgen exposure will make the largest contribution to in-dividual plasticity, but suggest that there may be additional effects at later developmental stages—particularly middle childhood and ado-lescence.

4.1. Potential mechanisms

In principle, androgens could increase plasticity through a range of developmental and molecular pathways. In a sexually dimorphic spe-cies like humans, phenotypic development of sexually selected traits (e.g., a taller body, larger muscles) targets more extreme values in males than in females. When developmental processes "aim high," the endpoint of the trajectory becomes more contingent on the availability of energetic resources and other factors that may interfere with devel-opmental processes (e.g., nutritional stress or infections; Kuzawa and Bragg, 2012). On a mechanistic level, androgens could shift the target of developmental trajectories through their interactions with other key endocrine systems involved in metabolism and growth—for example, the hypothalamic-pituitary-adrenal axis, the hypothalamic-pituitary-thyroid axes, or the insulin/insulin-like growth factor 1 (IGF-1) sig-naling system (Lancaster and Sinervo, 2011). This idea fits well with models of sexually selected condition dependence, and may help frame the role of androgens in the development of metabolically costly and/or developmentally fragile traits (e.g., height, muscularity). However, many other traits that show greater variability in males—such as per-sonality and sociosexuality—do not have obvious metabolic costs and are more likely to reflect alternative behavioral and reproductive stra-tegies.

Another way in which androgens might modulate plasticity in re-sponse to environmental cues is by affecting the development of basic temperamental traits such as negative affectivity and emotional re-activity; elevated levels of these traits have been found to increase susceptibility to the environment in infancy and early childhood (see Belsky, 1997; Belsky, 2005; Belsky and Pluess, 2009; Slagt et al., 2016). Indeed, there is initial evidence that prenatal and early postnatal levels of testosterone predict increased fear reactivity and negative affectivity in boys (Alexander and Saenz, 2011; Bergman et al., 2010; note that both of these studies had relatively small sample size and thus may have missed weaker effects of androgens in girls). In principle, androgens could affect temperament through a wide range of pathways, including through their interactions with dopamine, serotonin, oxytocin, and other neurotransmitters/neuromodulators that contribute to regulate an individual's sensitivity to external inputs (see Moore and Depue, 2016).

Still another potential mechanism for the action of androgens is upregulation of neural plasticity in the brain (e.g., synapse formation and remodeling). By increasing plasticity in brain development, an-drogens could broaden the range of an individual's long-term beha-vioral adjustments to contextual cues. While it is important to clearly differentiate between neural plasticity at the cellular level and devel-opmental plasticity at the level of phenotypic traits, the two are likely to overlap when one considers the development of behavioral traits such as personality and intelligence. There is considerable evidence from nonhuman studies that testosterone and other androgens (e.g., DHEA and DHEAS) promote cell proliferation, synapse formation, and dendritic growth in various brain regions, including the hippocampus, amygdala, and areas of the cortex (Campbell, 2006; García-Segura, 2009; MacLusky et al., 2006). Some of these effects may be mediated through conversion of androgens to estrogens within the brain, parti-cularly in females (reviewed in Fester and Rune, 2015; García-Segura,

2009). Of course, the idea that androgens have the net effect of in-creasing neural plasticity does not negate the existence of more com-plex patterns of action, including sex-specific effects of androgens and estrogens on different brain mechanisms (see Azcoitia et al., 2017; Fester and Rune, 2015)

In humans, males show increased expression of several genes in-volved in neuroplasticity during fetal development and infancy (e.g., Kang et al., 2011; Weickert et al., 2009). Upregulated brain plastici-ty—particularly compensatory plasticity in response to mutations that disrupt early neural development—has been proposed as an explana-tion for the higher prevalence of autism in males (Mottron et al., 2015). Another indication that androgens promote brain plasticity in our species comes from research on patient recovery from traumatic brain injury and stroke. Several large studies and meta-analyses have found that, contrary to early anecdotal reports and small-scale findings, men tend to recover faster from brain injury and show fewer residual symptoms than women (Bazarian et al., 2010; Broshek et al., 2005; Di Carlo et al., 2003; Farace and Alves, 2000; Gargano and Reeves, 2007). Taken together, these findings lend preliminary support to the idea that androgen-dependent neural plasticity may contribute to amplify the effect of environmental influences, with implications for both sex and individual differences.

4.2. Adaptive or maladaptive plasticity?

If exposure to androgens increases plasticity in traits with greater male variability, one can ask to what extent this effect is biologically adaptive (i.e., fitness-enhancing) or rather a non-adaptive or mala-daptive byproduct, for example an undesirable side effect of physical and behavioral masculinization. Existing evolutionary models differ in their implications: while some assign a larger role to vulnerability and decanalization (e.g., Geary, 2015, 2016), others emphasize the poten-tial for adaptive plasticity or phenotypic matching through bet-hedging (e.g., Bribiescas et al., 2012; Kuzawa et al., 2010; Rowe and Houle, 1996). At present, the empirical evidence is clearly insufficient to re-solve this issue. However, we wish to emphasize that the question of adaptiveness is unlikely to have a simple or straightforward answer, even as more and better evidence becomes available. This is because when the adaptive function of a trait involves an increase in phenotypic variability, the average effect of that trait on developmental outcomes may not be a good indicator of its net contribution to fitness. For ex-ample, to the extent that they operate in humans, bet-hedging strategies are only adaptive from the standpoint of the whole genetic lineage across generations, because random variation often leads to mis-matched phenotypes and fitness costs for individual organisms (Starrfelt and Kokko, 2013). The adaptive nature of bet-hedging cannot be detected by looking at the reproductive outcomes of single in-dividuals, and may take several generations to become apparent.

Similarly, high-risk strategies increase the variance of individual outcomes, effectively trading a smaller benefit for the opportunity of a larger but uncertain reward. Such strategies (e.g., physical aggression, overt dominance-seeking) can be adaptive even if most individuals suffer a fitness cost, provided that the few individuals who succeed enjoy a large enough benefit (reviewed in Frankenhuis and Del Giudice, 2012). Importantly, alternative reproductive strategies and condition-dependent displays embody a degree of risk-taking, and can be ex-pected to result in a mixture of individually adaptive and maladaptive outcomes. For these reasons, teasing apart the adaptive and maladap-tive components of androgen-dependent plasticity will require a con-siderable amount of evidence and careful analysis of alternative evo-lutionary explanations.

5. Future directions

There are many ways to start testing our hypothesis against the empirical data. To begin, the hypothesis inspires a straightforward

prediction: namely, that higher exposure to androgens during prenatal and early postnatal development (and possibly at later stages, such as puberty) should correlate with greater phenotypic variability in traits that show greater male variance. The crucial problem in this kind of study will be to reliably measure early androgen exposure. In particular, researchers should be careful about using *digit ratios* (typically the ratio between the length of the second and fourth finger, or 2D:4D) as proxies of prenatal androgen levels. Even if digit ratios are influenced by androgen exposure (Manning et al., 2014; Zheng and Cohn, 2011), the measure they provide is indirect and noisy, and very large samples are needed to achieve sufficient statistical power. Indeed, even large, well-powered studies have failed to demonstrate relationships between 2D:4D and masculine adult traits like stature, muscle or strength (Georgiev et al., 2017). Studies in which 2D:4D ratios were correlated to androgen and estrogen levels in maternal plasma, amniotic fluid, and umbilical cord blood have found small and often non-significant associations (Hickey et al., 2010; Hollier et al., 2015; Ventura et al., 2013).

Given these limitations, more direct measures of prenatal exposure (such as androgens in the amniotic fluid) may offer a more fruitful approach (Cohen-Bendahan et al., 2005). Similarly, there is evidence that females exposed to a male co-twin are passively exposed to high prenatal testosterone levels, and show evidence for masculinization of postnatal behavioral phenotypes (Tapp et al., 2011). Opposite sex co-twin designs have been used to assess the long-term effects of prenatal testosterone exposure in females, and could be extended to test hypotheses about variability and differential susceptibility. The less-studied early postnatal surge in testosterone in newborn males (the so-called "mini-puberty"), for which there is evidence for a range of long-term effects on both behavior and bodily traits (Lamminmäki et al., 2012; Kuzawa et al., 2010), is amenable to more direct measurement in urine samples, opening up opportunities for direct assessment of the possible plasticity-enhancing effects of androgen exposure during this early developmental window (Kuiri-Hänninen et al., 2014). Finally, the *anogenital distance* is an indirect anatomical measure of prenatal exposure to androgens that seems to be more sensitive and reliable than digit ratios (Dean and Sharpe, 2013; Thankamony et al., 2016).

A more complete test of our hypothesis will require the analysis of two-way interactions between androgen exposure and specific environmental factors, which is the classic design of differential susceptibility studies (Belsky et al., 2007). Again, sample size is a major concern in this kind of work: recent simulations indicate that testing interactions for differential susceptibility using standard methods requires considerably larger samples than previously assumed (Del Giudice, 2017b; for alternative methods see Widaman et al., 2012). Testing for sex differences in the effects of androgens on plasticity implies a focus on three-way interactions, with the resulting need for even larger samples. Collecting multiple indicators of androgen exposure and environmental quality would allow researchers to fit latent variable models to the data, and help maximize power by correcting for the marked unreliability of most hormonal and environmental measures.

Finally, perhaps the simplest way to begin to evaluate the hypothesis would be to test for differences in susceptibility between males and females as groups, without measuring individual variation in androgen exposure. Such group-level differences in environmental susceptibility would be consistent with increased plasticity through androgen exposure, but of course would not rule out other potential contributing factors (e.g., differential treatment by sex). In its simplest form, this design only requires testing a two-way interaction between sex and the relevant environmental variable. Another advantage is that existing data sets in which sex was only used as a covariate could be easily reanalyzed with a focus on sex differences in plasticity. It is worth restating that we do not expect that boys will *always* show higher plasticity: the prediction specifically applies to traits that show greater male variance, and admits exceptions for traits and environmental factors that are particularly relevant to female reproductive strategies (e.g.,

puberty timing, social support). A systematic examination of multiple traits and environmental variables across studies would provide a useful map of sex differences in plasticity—a map that could then be evaluated against evolutionary models of mating and reproductive strategies in humans.

If empirically supported, our hypothesis could open the way to a range of novel and intriguing research directions. Sex hormones in pregnancy are produced by two distinct and interacting individuals, the mother and the fetus (the placenta, which has broad endocrine functions, is a fetal organ). While the relations between maternal and amniotic levels of sex hormones are still unclear (Kuijper et al., 2013; van de Beek et al., 2004), maternal secretion of androgens may plausibly affect overall fetal exposure, especially in female fetuses. In principle, this creates the potential for (partial) conflicts of interests between the mother and fetus about the optimal level of plasticity after birth (Del Giudice, 2015a). The idea of prenatal conflicts about postnatal plasticity is speculative but potentially fertile. One possibility is that mothers are selected to favor higher levels of plasticity—and hence, if our hypothesis is correct, higher fetal exposure to androgens—because highly plastic children are also more susceptible to maternal influences. In other words, a mother who increases the plasticity of her offspring beyond the offspring's optimal point may be able to shape their development in ways that maximize *her* fitness (see Del Giudice, 2012, 2015a). This argument has been applied to potential conflicts about prenatal exposure to cortisol and other stress-related hormones (Del Giudice, 2012). The existence of physiological conflicts surrounding androgen exposure might help explain the intricate mechanisms that regulate the production and transfer of sex hormones during gestation.

6. Conclusion

As the idea that infants and children vary in their susceptibility to the environment has become more widely appreciated, researchers have sought to identify the genetic and physiological factors that determine individual differences in plasticity (Belsky and Pluess, 2009, 2013; Ellis et al., 2011; Moore and Depue, 2016). Building on principles from evolutionary biology and multiple lines of evidence, we advanced a novel hypothesis: for the majority of traits that show greater male variability, exposure to higher androgen levels during prenatal and early postnatal development (and possibly at later stages such as middle childhood and adolescence) should increase individual plasticity in both sexes. Since exposure to androgens is itself a function of both genetic and environmental influences, androgens could represent one of the pathways through which plasticity is adaptively calibrated in response to local conditions (see Del Giudice, 2015a, 2016; Dingemanse and Wolf, 2013).

Our hypothesis reaches beyond the standard set of physiological and neurobiological candidates for plasticity-enhancing factors, which include stress-related hormones such as cortisol and a number of central neurotransmitters/neuromodulators such as dopamine, serotonin, and oxytocin (Belsky and Pluess, 2013; Ellis et al., 2011; Moore and Depue, 2016). We stress that this hypothesis has been formulated *a priori*, not as a post-hoc explanation for a particular set of findings; its logic depends on several interlocking assumptions, which are individually plausible but susceptible to falsification. For these reasons, it is also a "risky" hypothesis that may or may not be confirmed by empirical research. If our predictions are supported, they hold promise to significantly expand our understanding of human development and pave the way for new and exciting research, with many potential applications to both normal and pathological development.

Conflict of interest

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