

Vantage Sensitivity: Environmental Sensitivity to Positive Experiences as a Function of Genetic Differences

Michael Pluess

Queen Mary University of London

Abstract

A large number of gene–environment interaction studies provide evidence that some people are more likely to be negatively affected by adverse experiences as a function of specific genetic variants. However, such “risk” variants are surprisingly frequent in the population. Evolutionary analysis suggests that genetic variants associated with increased risk for maladaptive development under adverse environmental conditions are maintained in the population because they are also associated with advantages in response to different contextual conditions. These advantages may include (a) coexisting genetic resilience pertaining to other adverse influences, (b) a general genetic susceptibility to both low and high environmental quality, and (c) a coexisting propensity to benefit disproportionately from positive and supportive exposures, as reflected in the recent framework of vantage sensitivity. After introducing the basic properties of vantage sensitivity and highlighting conceptual similarities and differences with diathesis–stress and differential susceptibility patterns of gene–environment interaction, selected and recent empirical evidence for the notion of vantage sensitivity as a function of genetic differences is reviewed. The unique contribution that the new perspective of vantage sensitivity may make to our understanding of social inequality will be discussed after suggesting neurocognitive and molecular mechanisms hypothesized to underlie the propensity to benefit disproportionately from benevolent experiences.

Quantitative behavioral genetics studies consistently report that heritable factors account for a large proportion of the variance of most psychological traits. For example, twin study–based heritability estimates for stable negative emotionality have been found to explain 40–50% of the population variance (Eaves et al., 1999; Jang, Livesley, & Vernon, 1996; Plomin, Owen, & McGuffin, 1994). Furthermore, it is also well established that individual differences in such heritable psychological traits can moderate the response to contextual factors. For example, harsh parenting has more adverse effects on children who score high on negative emotionality compared to those scoring low on the same trait (Belsky, Hsieh, & Cmic, 1998). Significant advances in molecular genetics over the last 15 years have allowed researchers to combine (a) the observation that individual differences in common psychological traits have a genetic basis with (b) the notion that some of these heritable psychological traits moderate the effects of environmental exposures through the study of gene–environment interaction (GXE). In the first-ever published GXE study, Caspi et al. (2002) were able to show that a specific genetic variant located in the *monoamine oxidase A* (MAOA) gene, which has been associated with aggression in previous linkage studies (Brunner, Nelen, Breakefield, Ropers, & van Oost, 1993), influenced whether children who were mal-

treated in childhood developed antisocial behavior in adulthood (for a meta-analysis of GXE studies involving MAOA, see Kim-Cohen et al., 2006; Taylor & Kim-Cohen, 2007). Over the last decade, a large number of similar studies emerged providing empirical evidence that genetic variation at multiple locations across the genome interacts with different aspects of the psychosocial environment in the prediction of various psychological outcomes (for a review, see Caspi & Moffitt, 2006; Manuck & McCaffery, 2014; Rutter, Moffitt, & Caspi, 2006). The majority of these GXE studies—particularly those published in the first 4–5 years following the seminal reports by Caspi et al. (2002, 2003)—focused almost exclusively on testing genetic vulnerability to the negative effects of adverse experiences regarding the development of psychopathology. However, more recent frameworks approach the notion of GXE from an evolutionary

I would like to thank Stephen Manuck for providing the term *vantage sensitivity* and acknowledge Jay Belsky's contribution to previous coauthored publications on vantage sensitivity, upon which some parts of the current article are based.

Correspondence concerning this article should be addressed to Michael Pluess, Department of Biological and Experimental Psychology, School of Biological and Chemical Sciences, Queen Mary University of London, Mile End Road, London E1 4NS, United Kingdom. Email: m.pluess@qmul.ac.uk.

perspective rather than one of psychopathology, proposing that individual differences in response to environmental influences should also emerge in response to positive benign exposures (Belsky & Pluess, 2013; Pluess & Belsky, 2013). In other words, genetic factors are likely to predict individual differences in environmental sensitivity *across the whole range of contextual quality*, not just in response to adverse or traumatic experiences (Pluess, 2015). In summary, genetic factors not only account for individual differences in psychological traits but also predict whether people are more or less affected by both adverse and supportive environmental exposures.

In what follows, I will draw on evolutionary reasoning in order to suggest that differences in environmental sensitivity as a function of common gene variants extend across a wide range of environmental quality, reflected in a number of distinct interaction patterns, including vantage sensitivity, which describes the moderation of positive effects of benign contextual influences (Pluess & Belsky, 2013). After presenting the relatively recent framework of vantage sensitivity, I will review selected empirical evidence for vantage sensitivity as a function of various common gene variants. Finally, I will discuss questions regarding the neurocognitive and molecular mechanisms hypothesized to underlie the propensity to benefit disproportionately from benevolent experiences, before suggesting implications and proposing how the notion of vantage sensitivity applies to questions pertaining to social inequality.

EVOLUTIONARY ANALYSIS OF GENE-ENVIRONMENT INTERACTION FINDINGS

A large number of empirical studies in the fields of developmental psychopathology and psychiatry provide empirical evidence for the notion that some people are more vulnerable to adversity due to their genes (Rutter et al., 2006), although it has to be acknowledged that much of this evidence is limited by underpowered samples and often characterized by inconsistent replication efforts (for reviews, see Duncan & Keller, 2011; Karg, Burmeister, Shedden, & Sen, 2011; Munafò et al., 2009; Risch et al., 2009; Uher & McGuffin, 2010). What the majority of these GXE studies have in common is that they typically find that carriers of a specific gene variant are more likely to succumb to the negative effects of environmental adversity, whereas carriers of an alternative gene variant appear to be resilient to the same adverse condition. Importantly, in most cases, the gene variant found to increase the risk for a maladaptive outcome in the presence of adversity tends to be unrelated to the negative outcome in the absence of said adversity. Consequently, such findings are consistent with a diathesis-stress or dual-risk perspective of person-environment interaction (Gottesman & Shields, 1967; Monroe & Simons, 1991; Zuckerman, 1999), according to which a negative outcome emerges only when an individual's vulnerability (e.g., a specific genetic variant) is combined

with an external stress factor. This view suggests that carrying gene variants (i.e., alleles) associated with resilience to adversity should be considered advantageous, whereas "risk" alleles present a liability and consequently a disadvantage. Application of evolutionary theory to this diathesis-stress perspective on GXE findings would—at first sight—predict that gene variants conferring risk for maladaptive psychological development in the context of adverse environmental conditions should be eliminated from the gene pool by process of natural selection given recent empirical evidence that people with certain psychological disorders have, on average, significantly fewer children and are therefore less likely to pass their genes into future generations (Bundy, Stahl, & MacCabe, 2011; Power et al., 2013). However, in contrast to this theoretical and reasonable hypothesis, the majority of the genetic risk variants examined in GXE studies have, in fact, a surprisingly high frequency in the general population (on the basis that a genetic variant is considered "common" if carried by more than 1% of the population). For example, the short allele of the *serotonin transporter* gene polymorphism (5-HTTLPR), which has been found to significantly increase the risk for depression in the context of early adversity (Karg et al., 2011), is carried by 25–80% of individuals depending on their ethnic background (Chiao & Blizinsky, 2010). The frequency of the *dopamine receptor D4* (DRD4) gene 7-repeat allele, which has been associated with heightened vulnerability for the development of externalizing behavior problems in response to insensitive parenting (Bakermans-Kranenburg & van IJzendoorn, 2006), ranges from 16% to 96% across different ethnicities (Chang, Kidd, Livak, Pakstis, & Kidd, 1996). Other gene variants that have been investigated widely in GXE studies have similar high frequencies: MAOA low-activity allele, 30–60%; *catechol-o-methyltransferase* (COMT) Val allele, 70–90%; *brain-derived neurotrophic factor* (BDNF) Met allele, 20–70%; and *dopamine receptor D2* (DRD2) A1 allele, 30–70%. Observations of such high risk-allele frequencies challenge the traditional diathesis-stress conceptualization that certain gene variants predominately have a risk function.

One conclusion given the surprisingly high frequencies of many genetic variants associated with increased risk for maladaptive development under adverse environmental conditions is that such putative genetic risk variants are maintained in the population because they are also associated with reproductive advantages, most probably in response to different contextual conditions (Uher, 2009). In other words, the liability of a genetic variant associated with increased vulnerability under some conditions may be balanced by advantages associated with the same variant in alternative conditions. Such advantages could take different forms, as I will discuss below. However, before considering this intriguing possibility further, it is important to acknowledge alternative evolutionary explanations for the high population frequency of risk alleles. For example, gene variants associated with risk today may have been adaptive in ancestral times, and the hypothesized

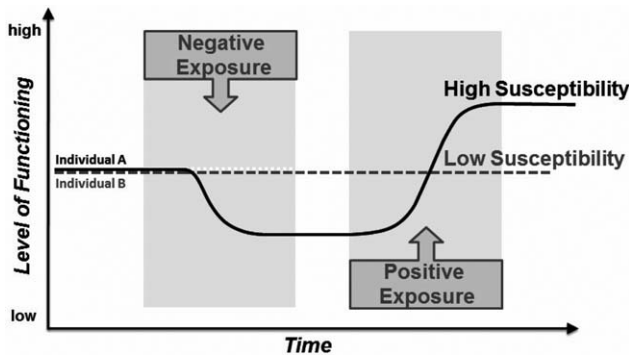


Figure 1 Graphical illustration of differential susceptibility: high susceptibility is characterized by increased environmental sensitivity as a function of genes (or other inherent characteristics) in response to both negative and positive exposures, whereas low susceptibility reflects relative psychological inertia to environmental influences independent of their quality (based on Pluess & Belsky, 2015, Figure 2).

reason they are still common today is that natural selection is a slow process, particularly for genes with only moderate to small effects on reproductive fitness. However, although this is a reasonable hypothesis that may apply to some gene variants, studies investigating selection processes suggest that the frequency of at least some of the studied gene variants has actually increased in recent history, which points toward a positive rather than a negative selection process (e.g., *DRD4* 7-repeat allele; Ding et al., 2002; Vallender & Lahn, 2004).

There are at least three different but not mutually exclusive reasons why genetic variants that are traditionally associated with increased risk for the development of problematic outcomes under adverse environmental conditions are maintained in the population. All of these suggestions propose that common “risk” gene variants also confer advantages under different contextual conditions.

Vulnerability Counterbalanced by Resilience

As described earlier, the diathesis-stress framework presumes that in GXE studies, some individuals are more vulnerable to the *adverse* effects of *negative* experiences and exposures due to a genetic “vulnerability,” whereas others are protected from the same adverse influences as a function of genetic “resilience.” Consequently, the first explanation for the high frequency of common gene variants that have been identified as “risk alleles” is that in some cases, the same variant that confers genetic vulnerability in one context (or regarding one particular outcome) may also confer genetic resilience in a different context (or regarding a different outcome). In other words, the same gene variant may be associated with *both* vulnerability *and* resilience depending on the specific environmental context or the specific outcome. One example from the medical field that reflects this combined effect of coexisting and counterbalanced vulnerability and resilience is found in the gene variant that causes sickle-cell disease. Individuals carrying the sickle-cell disease allele are

generally at greater risk of developing a range of serious health problems, but at the same time, they are also more resilient to malaria, which leads to a selective advantage for individuals carrying this allele in countries where malaria is prevalent and, hence, explains the relatively high population frequency of this particular risk allele (Luzzatto, 2012). Consequently, the disadvantage of a gene variant in one context can be counteracted or balanced by the advantage of the same variant in a different context or regarding a different, more adaptive outcome.

Differential Susceptibility

A second explanation for the high population frequency of putative risk alleles is that some of these “risk alleles” are not just increasing an individual’s vulnerability to low environmental quality but environmental sensitivity more generally, including heightened responsiveness to the positive effects at the upper end of environmental quality. Importantly, the diathesis-stress model makes no predictions regarding variation in response to putatively positive experiences besides suggesting—at least implicitly—that no differences are to be expected between genetically vulnerable and resilient individuals in the absence of adversity. However, an alternative model of environmental action has recently been advanced—differential susceptibility—suggesting that some individuals are disproportionately susceptible to both negative *and* positive experiences and environmental exposures (Belsky, 1997a, 2005; Belsky, Bakermans-Kranenburg, & van IJzendoorn, 2007; Belsky & Pluess, 2009a, 2013; Ellis, Boyce, Belsky, Bakermans-Kranenburg, & van IJzendoorn, 2011). According to differential susceptibility reasoning, more susceptible individuals are not just especially “vulnerable” to adversity but are more sensitive across the range of environmental quality (Belsky & Pluess, 2009b; Boyce & Ellis, 2005; Ellis et al., 2011). Thus, many of those whom the diathesis-stress framework considers disproportionately likely to be adversely affected by negative experiences and exposures may also be disproportionately likely to benefit from supportive and enriching ones. Consequently, differential susceptibility thinking encompasses both a “dark side” of environmental sensitivity, which refers to the increased susceptibility to negative experiences (i.e., vulnerability), and what Bakermans-Kranenburg and van IJzendoorn (2011) have labeled the “bright side,” or increased susceptibility to positive experiences and exposures (see also Homberg & Lesch, 2011). Applied to GXE studies, the differential susceptibility framework suggests that certain gene variants may increase an individual’s susceptibility to both negative *and* positive environmental influences (see Figure 1) rather than just to negative ones (Belsky et al., 2009). Consequently, carriers of susceptibility gene variants may indeed be more vulnerable to the negative effects of adverse experiences but will also benefit disproportionately from supportive exposures, which explains the relatively high population frequencies of gene variants investigated in GXE studies informed by diathesis-stress thinking.

Importantly, whereas diathesis-stress is primarily the result of empirical observations, the differential susceptibility framework has been derived theoretically from the following evolutionary considerations (Belsky, 1997b, 2005; Belsky & Pluess, 2009a, 2013): (a) Humans are characterized by a capacity for developmental plasticity that allows them to be shaped by their early environment in ways presumed to prepare them to function well in the environment they are likely to encounter in adulthood. (b) However, because the future is inherently uncertain, there is always a risk that future environmental conditions would prove rather different from those experienced earlier in life. The resulting mismatch between the developmentally influential early environment and future environmental conditions during the reproductive years would mean that the individual would be poorly prepared to succeed, especially reproductively, later in life. (c) Hence, natural selection should have engaged in a process of “bet hedging,” with some individuals proving developmentally plastic and some less so. That way, the negative consequences of a discrepancy or mismatch between the early environment and its developmental sequelae and the actual future environment would, theoretically, undermine the reproductive success of only those individuals who are more susceptible to the formative effects of early environmental influences (i.e., those with a higher degree of environmental sensitivity), but not those generally less susceptible. However, when environmental conditions remain stable, those who are more susceptible will have the advantage of being better adapted to the environment.

These evolutionary considerations provide the theoretical rationale for the proposition that moderation effects of common gene variants reflect general environmental sensitivity rather than exclusive vulnerability. The notion that carriers of such gene variants are not only more negatively affected by low environmental quality but also benefit significantly more from high environmental quality provides a plausible explanation for the high frequencies of putative genetic risk variants in the general population.

Vulnerability Counterbalanced by Vantage Sensitivity

The third reason why some of the gene variants associated with increased vulnerability to adversity are so frequent in the general population is that some of these risk alleles also increase the propensity of individuals to benefit from supportive environmental influences. In other words, the same variant that confers genetic vulnerability in an *adverse context* (or regarding one particular outcome) may also confer increased susceptibility to the positive influences experienced in a *different positive context* (or regarding a different outcome). Please note that differential susceptibility proposes individual differences in environmental sensitivity across the quality range of *one particular environmental context* (e.g., low to high parenting quality).

As it turns out, until recently, little empirical effort has been directed toward the investigation of genetic factors associated with the propensity to benefit from supportive, nurturing, or even just benign environmental conditions. One reason that such genetic moderation of positive aspects of the environment has not received much attention within the scientific community conducting GXE studies may be the lack of adequate frameworks that provide a solid theoretical rationale for the expectation of such variability (but see Shanahan & Hofer, 2005, for a discussion of gene-environment interaction in “enhancing” social contexts). Furthermore, while there is specific language to describe individuals who are more or less affected by adversity (i.e., “vulnerability” and “resilience,” respectively), terminology for those more or less responsive to positive aspects of the environment as a function of inherent characteristics is difficult, if not impossible, to find. These conceptual and semantic shortcomings within psychology have recently been addressed with the proposition of vantage sensitivity, a new concept with accompanying terminology for individual differences in response to positive experiences and environmental advantages (Manuck, 2011; Pluess & Belsky, 2013; Sweitzer et al., 2012): (a) *Vantage sensitivity* refers to the general proclivity of an individual to benefit from positive and presumptively well-being- and competence-promoting features of the environment, just as *vulnerability* depicts the tendency to succumb to negative effects of adversity in the diathesis-stress framework. (b) The degree of vantage sensitivity is a function of the presence of *vantage sensitivity factors* (i.e., promotive factors), just as *vulnerability/risk factors* increase vulnerability to negative effects of adversity in the diathesis-stress framework. Vantage sensitivity factors are by definition inherent characteristics of the individual, including genetic, physiological, and psychological traits, even if the focus of interest in this article is on genetic factors. (c) *Vantage resistance* describes the failure to benefit from positive influences, just as *resilience* characterizes the “failure” to succumb to the negative effects of adversity in the diathesis-stress framework. (d) The degree of vantage resistance is a function of the presence of vantage resistance factors or absence of vantage sensitivity ones, just as protective factors increase resilience to negative effects of adversity in the diathesis-stress framework.

In summary, vantage sensitivity factors increase vantage sensitivity, that is, susceptibility to the beneficial effects of positive experiences and exposures, whereas vantage resistance factors diminish or even completely eliminate positive response to the same supportive conditions (see Figure 2 for a graphical illustration).

Vantage sensitivity reflects the “bright side” of general environmental sensitivity as captured in the differential-susceptibility framework. However, vantage sensitivity is not synonymous with differential susceptibility, which describes environmental sensitivity along one specific contextual dimension ranging from low to high quality (e.g., low parenting quality to high parenting quality). It is conceivable that some genetic variants increase sensitivity to the higher end of a particular environmental influence but not vulnerability at the lower end of

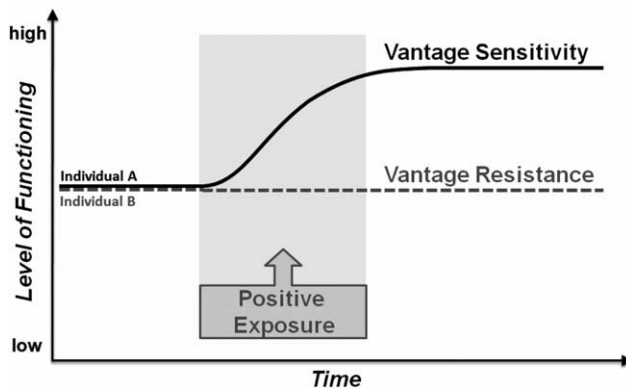


Figure 2 Graphical illustration of vantage sensitivity: vantage sensitivity describes the propensity to respond favorably to positive experiences, as a function of genetic (or other inherent) characteristics, whereas vantage resistance reflects the inability to benefit from supportive influences. The vantage sensitivity framework makes no predictions about individual differences in the absence of positive exposures (based on Pluess & Belsky, 2015, Figure 3).

the same dimension. Consequently, there are two possibilities accounting for how potential vantage sensitivity properties of certain common gene variants contribute to high population frequencies of putative “risk alleles.” First, as mentioned in the previous section, some gene variants may reflect general environmental sensitivity, which suggests that vantage sensitivity features of a particular gene variant at the upper end of environmental quality (e.g., high parenting quality) may counterbalance vulnerability properties of the same variant at the lower end of the same environmental influence (e.g., low parenting quality) so that disadvantages and advantages between individuals cancel each other out and the variant is maintained in the population. Second, vantage sensitivity associated with a gene variant in one particular context (or regarding one specific outcome) may counteract vulnerability of the same variant in a different context (or regarding a different specific outcome). Hence, rather than reflecting general environmental sensitivity as conceptualized in the differential susceptibility framework, some gene variants may confer a combination of vulnerability and vantage sensitivity across different contexts/outcomes, which results in high population frequencies in spite of associated vulnerability (for a combination of vantage sensitivity and vulnerability as a function of the same gene variant but regarding different outcomes, see Sulik et al., 2014).

EMPIRICAL EVIDENCE OF VANTAGE SENSITIVITY

Given that vantage sensitivity is a relatively recent framework, empirical investigation of this particular pattern of genetic moderation is still in its early stages. While there is a large number of studies providing evidence for vantage sensitivity reflecting the bright side of differential susceptibility (for a detailed review of these studies, see Belsky & Pluess, 2009a, 2013), the combina-

tion of both vulnerability *in one context* and vantage sensitivity *in an alternative context* as a function of the *same* variant, as suggested earlier, has not been tested rigorously yet (but for examples of studies that investigated genetic moderation of both negative and positive environmental influences or in the prediction of both adaptive and maladaptive outcomes, see Luijk et al., 2011; Sulik et al., 2014, described in more detail in the empirical evidence section). However, a growing number of studies testing genetic differences in response to psychological intervention provide strong evidence that vantage sensitivity can be observed as a function of genetic factors. In what follows, I will review a selection of such studies. Before doing so, it is important to acknowledge that in the majority of the reviewed studies, the gene variants associated with increased response to supportive exposures have previously been found to also increase the response to negative exposures, suggesting that these genes reflect both the “dark” and “bright” sides of environmental sensitivity. Whether there exist gene variants exclusively associated with vantage sensitivity remains to be determined in future research.

Dopamine Receptor D4 (DRD4)

The dopaminergic system plays an important role in attentional, motivational, and reward processes, and a polymorphism of the *dopamine receptor D4* (DRD4) gene has been much studied in GXE research. Variants of the DRD4 differ by the number of 48-base pair tandem repeats, ranging from 2 to 11. The 7-repeat variant has been regarded as a vulnerability factor due to its links to attention deficit/hyperactivity disorder (ADHD; Faraone, Doyle, Mick, & Biederman, 2001), high novelty-seeking behavior (Kluger, Siegfried, & Ebstein, 2002), and low dopamine reception efficiency (Robbins & Everitt, 1999), among other correlates. Findings of a meta-analysis of GXE studies involving DRD4 and other dopamine-related genes and children under age 10 years indicate that those carrying less efficient dopamine-related genes, including the DRD4 7-repeat allele, are more vulnerable to negative environments but, supporting a differential susceptibility model, also show greater vantage sensitivity in response to positive environments (Bakermans-Kranenburg & van IJzendoorn, 2011). Intriguingly, vantage sensitivity-related effects—that is, responsiveness to supportive environmental experiences—proved stronger than diathesis-stress-related effects. In other words, the apparent benefits of carrying putative “risk” alleles in the face of environmental support or enrichment were greater than the apparent costs under conditions of contextual adversity. Several studies provide evidence for vantage sensitivity as a function of the DRD4 7-repeat allele. I will restrict my review to two more recent studies (for more examples, see Pluess & Belsky, 2013).

In the first study, Kegel, Bus, and van IJzendoorn (2011) investigated genetic sensitivity as a function of the DRD4 7-repeat in response to a computer-based literacy instruction program ($N = 182$ four- to five-year-old boys and girls). Two

intervention groups, one with positive feedback and one without, were compared to a control group on the development of emergent literacy skills. Only children carrying the DRD4 7-repeat variant increased their early literacy skills in response to the intervention (there were no differences between genotypes in the control condition). Notably, the positive effect of the intervention in children with the DRD4 7-repeat was restricted to the group that received positive feedback as part of the computer program. In the absence of positive feedback, there was no difference in literacy skills between children in the intervention or control groups, thereby suggesting that the presence of the DRD4 7-repeat allele predicted vantage sensitivity to the positive feedback component of the intervention.

In the second study involving DRD4, Cleveland et al. (2015) investigated in a randomized controlled trial whether DRD4 moderated the positive effects of an intervention program aimed at preventing underage alcohol use, among other things, in a sample of 545 adolescents. Although the interaction term between DRD4 and group assignment did not reach significance, the three-way interaction involving intervention assignment, maternal involvement, and DRD4 was significant. According to follow-up analyses, it was only adolescents who carried the DRD4 7-repeat allele, were assigned to the treatment condition, and also had highly involved mothers who were benefitting from the intervention. DRD4 7-repeat carriers who were assigned to the treatment group but whose mothers were not very supportive did not differ from similar adolescents assigned to the control condition. Importantly, adolescents without the DRD4 7-repeat allele did not benefit from the intervention regardless of mother involvement, suggesting that the DRD4 7-repeat allele increased vantage sensitivity to the potent combination of high maternal involvement and preventative treatment assignment.

Serotonin Transporter (5-HTTLPR)

A large proportion of GXE studies is based on genetic variants in the serotonergic system, most prominently the serotonin-transporter-linked polymorphic region (5-HTTLPR), which is a variable number tandem repeat (VNTR) polymorphic region in SLC6A4, the gene that codes for the serotonin transporter. Most research focuses on two variants, a short allele (S) and a long allele (L). The short allele has generally been associated with reduced transcriptional efficiency of the serotonin transporter—a protein involved in the reuptake of serotonin from the synaptic cleft—and thus considered to be related to depression, either directly (Munafò et al., 2009; Sen, Burmeister, & Ghosh, 2004) or in the face of adversity (Karg et al., 2011; Risch et al., 2009).

As it turns out, in a substantial proportion of relevant GXE studies, results are actually more indicative of differential susceptibility than diathesis-stress, with 5-HTTLPR short allele carriers having the worst outcomes under adverse conditions as well as the best outcomes under supportive conditions (Belsky et al., 2009; Belsky & Pluess, 2009a). For example, a meta-

analysis involving 2,276 Caucasian children under the age of 18 years showed that those with one or two short alleles were more negatively affected by adversity but also benefited more from positive environmental exposures than children without them (van IJzendoorn, Belsky, & Bakermans-Kranenburg, 2012). I will restrict my review to two exemplary studies.

Eley et al. (2012) tested whether 5-HTTLPR moderated the positive effects of cognitive-behavioral therapy for anxiety disorders in a sample of 359 six- to thirteen-year-old boys and girls. Clinical diagnoses of anxiety disorders and symptom severity were assessed before and after treatment, as well as 6 months after treatment ended. Although all children appeared to benefit from the treatment, the positive effect of the intervention at the follow-up assessment was particularly pronounced in the case of those children carrying the short allele (there was no difference in anxiety between genotypes at the pretreatment assessment). More specifically, those homozygous for the 5-HTTLPR short allele showed a significantly greater reduction in symptom severity from pretreatment to follow-up assessment, so much so, in fact, that they proved 20% more likely than others to be free of anxiety disorder at the 6-month follow-up assessment.

In the second example of vantage sensitivity as a function of 5-HTTLPR, Drury and colleagues (2012) applied a randomized controlled design in order to determine whether 5-HTTLPR would moderate the effect of early rearing condition on indiscriminate social behavior when children were 54 months old. In the Bucharest Early Intervention Project, 136 abandoned children between 6 and 30 months of age were randomly assigned to standard institutional care or a newly developed high-quality foster care program (Zeanah et al., 2003). Indiscriminate social behavior is regarded as a “signature consequence” of deprived institutional care. Children homozygous for the 5-HTTLPR short allele randomly allocated to the high-quality foster care condition had the lowest indiscriminate social behavior scores of the whole sample at 54 months, whereas for children with the 5-HTTLPR long allele there was no beneficial effect of high-quality foster care. Furthermore, children homozygous for the short allele who were allocated to standard institutionalized care showed only a modest increase in indiscriminate social behavior compared to those with the long allele, suggesting that Drury and colleagues’ (2012) findings are more consistent with vantage sensitivity than differential susceptibility, at least based on visual inspection of the graphic illustration of their results (see Drury et al., 2012, Figure 3).

Brain-Derived Neurotrophic Factor (BDNF)

A further example of vantage sensitivity emerged in a study by Felmingham, Dobson-Stone, Schofield, Quirk, and Bryant (2013) regarding the genetic moderation of the response to exposure therapy in the treatment of posttraumatic stress disorder (PTSD) as a function of a genetic polymorphism located in the *brain-derived neurotrophic factor* (BDNF) gene. All of the 55 included study participants with clinically

diagnosed PTSD underwent 8 weeks of exposure-based cognitive-behavioral therapy. Although all patients showed a significant pre-post decrease in PTSD symptoms, patients homozygous for the BDNF Val allele showed a 62% reduction, whereas patients with one or more Met alleles showed only a 40% reduction in PTSD symptoms, suggesting that the BDNF Val/Val genotype increased vantage sensitivity to exposure therapy in PTSD patients—by almost 50% (there was no difference in PTSD symptoms between genotypes at pretreatment).

Oxytocin Receptor (OXTR)

Pluess and Belsky (2015) conducted a small exploratory vantage sensitivity study to test whether a range of genetic variants moderated the positive effects of a school-based positive psychology program on measures of psychological well-being. Applying a growth curve model, they tested whether 71 eleven- to twelve-year-old children at the same state school in England differed in the benefit they derived from the SPARK Resilience Programme, a universal school-based resilience-promoting intervention (Boniwell & Ryan, 2009; Pluess, Boniwell, Hefferon, & Tunariu, 2015), as a function of genetic differences. Self-reported measures of life satisfaction (Huebner, 1991) were obtained before and after the 3-month intervention, as well as at a 6-month follow-up assessment. DNA was collected using cheek swabs and genotyped for a range of genetic variants hypothesized to moderate effects of positive environmental influences, including a genetic polymorphism in the *oxytocin receptor* gene (OXTR; rs2268498). Results were consistent with vantage sensitivity: Only children homozygous for the OXTR T-allele showed a significant increase in life satisfaction scores over the course of the intervention (there were no differences in life satisfaction between genotypes at the pretreatment assessment).

Glucocorticoid Receptor (NR3C1)

Investigating genetic moderation of the treatment effects of an intervention aimed at reducing externalizing behavior problems in at-risk adolescents ($N = 242$), Albert et al. (2015) tested whether a well-characterized polymorphism in the *glucocorticoid receptor* gene (NR3C1) predicted treatment effects 10 years after the intervention began when participants were 25 years old. Follow-up analysis of the significant interaction between NR3C1 and group allocation (randomized controlled trial) suggested that participants of European American descent carrying one or more NR3C1 A-alleles who were allocated to the treatment condition had a significantly reduced prevalence of externalizing disorders compared to all other participants. A-allele carriers allocated to the control condition had slightly more externalizing disorders, but this difference did not reach statistical significance. Individuals homozygous for the G-allele,

on the other hand, did not differ from each other whether they were allocated to the treatment or control condition. Hence, the study provides evidence for vantage sensitivity (rather than differential susceptibility) as a function of the NR3C1 A-allele.

FK506-Binding Protein (FKBP5)

Wilker et al. (2014) sought to investigate whether a genetic polymorphism in the *FK506-binding protein* (FKBP5; rs1360780), a protein that moderates the sensitivity of glucocorticoid receptors, predicted the response to exposure therapy in 43 adult survivors of the rebel war in Northern Uganda. PTSD symptom severity was assessed before and at 4 and 10 months after treatment completion. Applying a treatment-only design, the authors found that FKBP5 significantly moderated treatment efficacy. Similar to findings that emerged in Eley and colleagues' (2012) study, all participants showed a significant and similar decrease in PTSD symptoms between baseline and 4-month follow-up, irrespective of genotype (there was no difference in PTSD symptoms between genotypes at pretreatment assessment). However, participants homozygous for the FKBP5 C-allele continued to show improvements up to the 10-month assessment, in contrast to those with the T-allele, suggesting that the C-allele increased vantage sensitivity to exposure therapy in this particular population.

Opioid Receptor (OPRM1)

The notion that genetic factors may influence the positive response to mindfulness-based cognitive therapy has recently been tested by Bakker et al. (2014) in a randomized controlled trial involving 126 adults with residual depressive symptoms. A range of genetic polymorphisms known to be involved in reward functioning were selected. Correcting for multiple testing, several significant moderation effects of treatment efficacy emerged, including one involving a polymorphism located in the *opioid receptor* gene (OPRM1; rs495491). Consistent with a pattern of vantage sensitivity, carriers of the OPRM1 C-allele showed a significantly stronger increase in positive affect as a function of the intervention compared to those homozygous for the T-allele. Importantly, genetic differences were not associated with any differences in the control condition, which suggests the moderation patterns were consistent with vantage sensitivity rather than differential susceptibility.

Evidence From Nonexperimental Longitudinal Studies

Vantage sensitivity findings are not restricted to studies testing intervention effects. Similar patterns of genetic moderation of the positive effects of supportive environmental influences are also observable in longitudinal cohort studies. For example, in a longitudinal study involving 502 children and their mothers, Luijk and associates (2011) investigated whether a genetic

polymorphism located in the *mineralocorticoid receptor* (MR) gene moderated the effect of observer-rated maternal sensitivity on the child's attachment security at the age of 14 months, assessed with the Strange Situation Procedure. Consistent with vantage sensitivity, children carrying one or more G-alleles were more securely attached when mother's sensitive responsiveness was particularly high, whereas children homozygous for the A-allele were not affected by mother's sensitivity regarding their attachment security. Importantly, when maternal sensitivity was low, there was no difference in attachment security between children with different genotypes, suggesting that differences only emerged at the upper end of maternal sensitivity, consistent with vantage sensitivity rather than differential susceptibility (although the same genotype was also more negatively affected by extreme sensitivity measured with a different instrument).

A further example of vantage sensitivity as a function of genetic differences in a longitudinal study design is found in Sulik and colleagues' (2014) investigation of the effects of parenting quality on child inhibitory control featuring a sample of 146 families. COMT significantly moderated the effect of maternal parenting quality across early childhood on mother-rated inhibitory control at the age of 7 years. The genetic moderation as a function of COMT was further moderated by child gender. Girls with the COMT Val allele and boys homozygous for the Met allele showed higher inhibitory control compared to other genotypes when having experienced high-quality parenting. Yet at the lower end of parenting quality, there was no genetic moderation in the prediction of inhibitory control, suggesting that the observed interaction patterns were consistent with vantage sensitivity rather than differential susceptibility or diathesis-stress. However, boys homozygous for the Met allele also had significantly higher internalizing problems when parenting quality was low, consistent with a diathesis-stress pattern. This study demonstrates the importance of considering gender-specific effects as well as moderation effects on different outcomes.

CONCEPTUAL CONSIDERATIONS

Before discussing mechanisms and implications of vantage sensitivity as a function of genetic differences, it is important to highlight similarities and differences between vantage sensitivity and differential susceptibility. Although theoretically closely related to differential susceptibility, vantage sensitivity represents more than just the "bright side" of susceptibility given that some genes may increase sensitivity to the benefits of supportive environments while not necessarily making individuals also more vulnerable to the negative effects of contextual adversity (or not at the lower end of the same environmental dimension). Hence, in some instances, genetic differences in the response to environmental influences may emerge exclusively under supportive conditions—implying vantage sensitivity—rather than under both low and high quality along the same contextual dimension, which would imply differential susceptibility.

A further distinction to be made between vantage sensitivity and differential susceptibility pertains to the empirical conditions required to evaluate each. In order to investigate differential susceptibility, environmental quality must range from the negative to the positive extremes across the contextual domain of interest (Belsky et al., 2007; Belsky & Pluess, 2009a), which is not essential for testing vantage sensitivity. In fact, many truly positive exposures do not range from the positive to the negative but only from the positive to the absence of the positive (e.g., psychological intervention vs. no intervention), which means that genetic moderation of such exposures is consistent with vantage sensitivity—or the "bright side" of environmental sensitivity—rather than differential susceptibility.

VANTAGE SENSITIVITY GENES

According to current empirical evidence for vantage sensitivity, the majority of detected gene variants associated with vantage sensitivity appear to be the same variants that emerged repeatedly as "risk" or "differential susceptibility" alleles in the psychological and psychiatric literatures. The observation that many of these putative "risk alleles" are also associated with increased vantage sensitivity to positive effects of supportive environments supports the claim that in many cases these gene variants should be conceptualized as such reflecting environmental sensitivity rather than either vulnerability or vantage sensitivity (Pluess, 2015).

Consequently, it remains to be determined whether gene variants that confer both vulnerability to adversity and vantage sensitivity—whether along a continuum of one specific contextual dimension (i.e., differential susceptibility) or across various contexts (i.e., combined diathesis-stress and vantage sensitivity in different contexts, as suggested earlier)—can be differentiated from those that confer only one or the other. Although the same gene variants often seem to moderate effects of environmental influences whether they are exclusively negative (i.e., diathesis-stress), exclusively positive (i.e., vantage sensitivity), or both (i.e., differential susceptibility), it is important to caution against inferring that every risk variant will also, by default, have vantage sensitivity or differential susceptibility properties (although this is likely to be the case for common variants, as discussed earlier). In fact, there may be specific gene variants that play a predominant role in diathesis-stress but not in vantage sensitivity and vice versa.

The identification of gene variants associated exclusively with vantage sensitivity remains a central objective for future research. However, given that most phenotypic traits are the function of many gene variants of small effects rather than of a single or a few gene variants with large effects (Pluess & Meaney, 2015), vantage sensitivity is also most likely associated with multiple variants rather than a few candidate genes. Hence, future studies should extend methodology to include genome-wide approaches, including polygenic scores, rather than relying

on the same selection of gene variants that candidate gene studies tend to focus on.

MECHANISMS ACCOUNTING FOR VANTAGE SENSITIVITY

Given that individual genes code for proteins that affect cellular function rather than complex behavior, it is unlikely that there are gene variants that are directly and exclusively associated with vantage sensitivity or environmental sensitivity more generally. It is much more likely that certain gene variants influence so-called intermediate or “endophenotypic” neurobiological features (e.g., neurotransmitter systems in the brain) that are involved in a wide range of behavioral outcomes, including sensitivity to beneficial environmental influences. Hence, rather than directly moderating positive environmental effects, gene variants more likely contribute to higher-order systems associated with increased environmental sensitivity. The specific genes that have been identified in empirical studies may point to such higher-order biological systems involved in environmental sensitivity (e.g., serotonergic and dopaminergic neurotransmitter systems). Furthermore, although explicit efforts to identify mechanisms and processes of vantage sensitivity have not been undertaken yet, it is likely that there are multiple processes at work that can be studied at different levels of analysis (e.g., molecular, neurological, behavioral). These mechanisms may involve attentional processes (Beevers et al., 2011), reward sensitivity (Roiser, Rogers, Cook, & Sahakian, 2006), stress response sensitivity (Boyce & Ellis, 2005), and social sensitivity (Way & Taylor, 2010), to mention some of the most likely candidates based on existing candidate gene studies (for more details, see Pluess & Belsky, 2013). The fact that all these mechanisms are higher-order central nervous processes is consistent with the hypothesis raised by several authors (Aron, Aron, & Jagiellowicz, 2012; Belsky & Pluess, 2009a, 2013) that some individuals are more responsive to environmental influences than others because they have a more sensitive central nervous system on which experiences register more easily and deeply. According to this “neurosensitivity” hypothesis, some gene variants contribute to heightened sensitivity of specific brain regions, which then increase the response to environmental influences, including positive, supportive ones (Pluess, 2015; Pluess, Stevens, & Belsky, 2013). One brain region that seems very likely involved in vantage sensitivity (as well as environmental sensitivity more generally) is the amygdala, which plays an important role in the processing of emotional stimuli (Sander, Grafman, & Zalla, 2003), responds strongly to positive stimuli (Sergerie, Chochol, & Armony, 2008), and has been found to be more active in individuals carrying the 5-HTTLPR short allele (Munafò, Brown, & Hariri, 2008).

On the molecular level, very recent work suggests that some of the gene variants associated with vantage sensitivity—or more generally with environmental sensitivity—increase the propensity for environmentally induced genome-wide methyla-

tion, an epigenetic mechanism that regulates gene expression. For example, according to a recent study conducted by Beach et al. (2014), differential exposure to cumulative socioeconomic risk was associated with more genome-wide methylation differences in African American adolescents carrying the 5-HTTLPR short allele compared to those with the long allele. Similarly, Chen et al., (2015) found in their investigation of the relationships between maternal anxiety during pregnancy and genome-wide methylation in the cord blood of babies shortly after birth that maternal prenatal anxiety was associated with significantly higher levels of methylation across the whole genome in babies homozygous for the BDNF Met allele compared to those carrying the Val allele.

IMPLICATIONS OF VANTAGE SENSITIVITY

The notion of vantage sensitivity as a function of genetic differences provides a new and important perspective for research on GXE. Whereas the majority of early GXE studies relied on the traditional diathesis-stress model, more recent studies appear to increasingly apply a differential susceptibility perspective, which often describes the detected interaction patterns more adequately besides being more consistent with evolutionary considerations. However, until recently, concepts and terminology for the “bright side” of environmental sensitivity were missing. The framework of vantage sensitivity fills this gap (Pluess & Belsky, 2013). According to a large body of research, individual differences in environmental sensitivity come in different shapes and forms, and the three models—diathesis-stress, differential susceptibility, and vantage sensitivity—allow for a more precise description of the different possible sensitivity patterns (Pluess, 2015). Besides this more theoretical implication regarding variability in environmental sensitivity, vantage sensitivity suggests that positive effects of interventions aimed at benefiting people—whether individual psychotherapy, family- and school-based prevention programs, or national policy—may generally differ as a function of individual genetic differences. Although it is well known that treatment efficacy varies across people, until recently the field lacked theory and evidence for whether genetic factors might matter in this regard.

The emerging studies, reviewed earlier, showing that specific gene variants seem to predict differences in vantage sensitivity, provide evidence that genetic factors do play an important role in determining the positive response to beneficial environmental influences. At first sight, these findings may suggest that genetic screening could prove valuable in order to improve treatment, intervention, and policy efficacy. However, given that vantage sensitivity is most likely the function of many thousand gene variants of small effects rather than a few selected candidate genes, and that gene expression is further regulated by epigenetic factors in response to environmental influences (Pluess & Meaney, 2015; Szyf & Pluess, 2015), genetic screening does not appear to be a viable and reasonable approach—at least not based on

current knowledge. Rather, future studies should focus on identifying the different biological systems that play an important role in vantage sensitivity—using replicated vantage sensitivity gene networks as guides—in order to detect endophenotypes and higher-order systems associated with vantage sensitivity. Furthermore, while it is not possible to change an individual's genetic structure, it may be possible to promote increased responsiveness to positive effects of supportive programs through interventions specifically developed to target and strengthen higher-order characteristics associated with vantage sensitivity.

The observation of vantage sensitivity as a function of genetic differences suggests that individuals who carry vantage sensitivity gene variants are generally at an advantage compared to those without such variants. In other words, genetic differences may not only account for individual differences in vulnerability but also predict variability in the propensity to respond favorably to positive, supportive exposures and opportunities. Taken further, this suggests that such genetic differences in vantage sensitivity may also play an important role in widely observed social inequality. It is well known that many positive outcomes (e.g., health, education, income) are characterized by a social gradient, with quality of outcomes generally declining from the most to the least advantaged socioeconomic groups (e.g., Mackenbach et al., 2008). Recently, it has been shown that some of this social gradient is accounted for by personality traits that are known to have a heritable genetic basis (Pluess & Bartley, 2015). Hence, application of vantage sensitivity to the observation of social inequalities suggests that one of the many reasons some people are at higher risk of suffering disadvantages and less likely to experience upward social mobility is that they are biologically less able to benefit from opportunities. In other words, genetic vantage resistance may explain why some people remain socially disadvantaged, whereas genetic vantage sensitivity may explain why some people do well and show social mobility in response to conditions and experiences that provide opportunities for growth and improvement. Future work on social inequality will benefit from applying vantage sensitivity reasoning, taking into account not only direct genetic contributions to outcomes but also the genetic underpinnings of sensitivity to positive exposures and experiences.

In summary, the notion of vantage sensitivity suggests that individuals differ substantially in their ability to benefit from well-being-promoting experiences, interventions, and policies as a function of individual traits, including genetic factors. People characterized by genetic vantage sensitivity are significantly more likely to respond favorably to positive and supportive exposures, whereas those without such a genetic propensity are more likely to be resistant to the positive effects of beneficial environmental influences.

Glossary

Diathesis-Stress: Framework for individual differences in response to adverse experiences. Vulnerability (i.e., diathesis)

describes the propensity to respond negatively to adversity, whereas resilience reflects protective resistance from the same negative influence.

Differential Susceptibility: Framework for individual differences in general environmental sensitivity. High susceptibility is characterized by increased susceptibility in response to both negative and positive exposures, whereas low susceptibility reflects psychological inertia to environmental influences independent of their quality.

Vantage Sensitivity: Framework for individual differences in response to positive experiences as a function of inherent characteristics. Vantage sensitivity describes the propensity to respond favorably to positive experiences, whereas vantage resistance reflects the inability to benefit from supportive influences.

Declaration of Conflicting Interests

The author declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author received no financial support for the research, authorship, and/or publication of this article.

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