Title
Gene-environment interaction in evolutionary perspective: differential susceptibility to environmental influences.

Permalink
https://escholarship.org/uc/item/1mm6q03t

Journal
World psychiatry : official journal of the World Psychiatric Association (WPA), 13(1)

ISSN
1723-8617

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Publication Date
2014-02-01

DOI
10.1002/wps.20092

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By tradition, psychiatrists have been concerned with the nature, origins, sequelae and treatment of mental disorders. When it comes to etiology and the role of genetics, psychiatric geneticists have focused on genotype-phenotype associations, that is, direct links between particular polymorphisms and particular disorders, as well as genetic vulnerability to adversity, as revealed in studies of gene-environment interaction.

Here we offer a new way of looking at these psychiatric-genetic issues. Rather than conceptualizing some genetic polymorphisms as genes for some disorder or as functioning as “risk genes”, increasing the likelihood that disorder will emerge in the face of contextual adversity, we contend that many genes which have been the focus of psychiatric-genetic research may actually make people more vs. less sensitive to the environment and thus differentially susceptible to developmental experiences and environmental exposures.

Moreover, and contrary to prevailing thinking, we argue that select polymorphisms should be conceptualized as “plasticity” rather than “vulnerability” genes (1), making individuals not just more likely to succumb to mental disorders when they experience adversity, but more likely to benefit from supportive conditions and to be adversely affected by negative ones (2,3).

This way of conceptualizing gene-environment interaction derives from an evolutionary analysis of human development (1,3,4), one which explicitly acknowledges that there are both costs and benefits of plasticity, with some costs related to the fact that the future is inherently uncertain; as a result, sometimes, when prior developmental experience shapes later functioning, a costly “mismatch” will ensue, as the world encountered later in development proves inconsistent with that experienced at an earlier – and influential – point in time. This suggests that natural selection would have “hedged its bets”, making some individuals more and other less – or hardly at all – developmentally plastic. This further implies that developmental plasticity should be regarded as a phenotype or individual-difference construct in its own right (4).

As it turns out, many gene-environment interaction findings prove consistent with this view that some individuals are more affected – due to their genetic make-up – by environmental exposure in a “for-better-and-for-worse” manner (2), depending on the environment to which they are exposed. For illustrative purposes we here focus on two widely studied polymorphisms.

TWO PLASTICITY GENES?

Like other polymorphisms, the serotonin transporter gene, 5-HTTLPR, and the dopamine receptor gene, DRD4, have long been regarded by psychiatric geneticists as “vulnerability genes” predisposing carriers of particular alleles to depression and attention-deficit/hyperactivity disorder (ADHD), respectively, in the face of adversity. Ever more evidence indicates, however, that they might better be regarded as “plasticity genes”, making carriers of the putative risk alleles especially susceptible to environmental influences – for better and for worse.

Regarding 5-HTTLPR, individuals carrying one or more short alleles have been found to show greater “for-better-or-for-worse” plasticity when the rearing predictor and child outcome are, respectively, maternal responsiveness and moral internalization, child maltreatment and antisocial behavior, and supportive parenting and positive affect. Such differential-susceptibility-related findings also emerge (among male African-American adolescents) when perceived racial discrimination is used to predict conduct problems; when life events are used to predict neuroticism and life satisfaction of young adults; and when retrospectively reported childhood adversity is used to explain aspects of impulsivity among college students. In fact, a recent meta-analysis reveals that, in the case of Caucasian children under 18 years of age, short-allele carriers are more susceptible than long-allele carriers to both positive and negative developmental experiences (5).

Regarding DRD4, heightened if not exclusive susceptibility has emerged in the case of carriers of the 7-repeat allele in contexts where the environmental predictor and developmental outcome were, respectively, maternal positivity and prosocial behavior; early nonfamilial childcare and social competence; contextual stress and support and adolescent negative arousal; childhood adversity and young-adult persistent alcohol dependence; and newborn risk status (i.e., gestational age, birth weight for gestational age, length of stay in the hospital) and observed maternal sensitivity. Notable again is that a meta-analysis of gene-environment interaction research involving dopamine-related genes found that children 8 and younger respond to positive and negative experiences in a manner consistent with differential susceptibility (6).
FUTURE RESEARCH DIRECTIONS

Despite ever-growing gene-environment interaction evidence consistent with the plasticity-genes’ view under consideration, many issues remain to be explored or illuminated. In addition to 5-HTTLPR and DRD4, there is evidence that other well studied polymorphisms may operate as plasticity factors (e.g., brain-derived neurotrophic factor, BDNF; monoamine-oxidase A), rendering some individuals more susceptible to environmental influences – for better and for worse (4). Especially important to appreciate is that most polymorphisms that have emerged as potential plasticity factors derive from psychiatric-genetic studies guided by vulnerability thinking. Researchers should thus expand their list of candidate genes beyond such polymorphisms associated with disturbed functioning, ideally to ones thought to influence plasticity. A recent example of such an effort yielding evidence of differential susceptibility focused on the CHRNA4 genotype, because of its role in acetylcholine production, a component strongly related to plasticity and learning (7).

Rather than regarding some individuals as plastic or malleable (e.g., 5-HTTLPR short-allele carriers) and others as not (e.g., homozygous long-allele carriers), it probably makes more sense to think of a gradient, with some being especially malleable, some reasonably malleable, some less so, and some not at all. Certainly that is suggested by work using multiple plasticity genes, as it reveals a dose-response relation between number of plasticity genes and the extent to which individuals are affected by environmental exposures in a for-better-and-for-worse manner (4). Future work of this kind should be guided by a “system-level genetic approach” involving the compositing of putative plasticity genes based on knowledge of particular biological processes or pathways, such as the dopaminergic or serotonergic system, or neurological morphology.

Furthermore, most differential-susceptibility-related research has been observational in character. This can challenge interpretation because environmental experiences may be selected rather than randomly assigned, creating the possibility that gene-environment correlation masquerades as gene-environment interaction. One solution to this problem involves conducting intervention experiments with random assignment of participants to experimental or control conditions, a work still in its early stages (4.8). Even though such efforts are limited to examining just the “for-better” side of plasticity, they still enable evaluation of whether allelic variants observed to make individuals especially vulnerable to adversity in observational research also predispose carriers to benefit disproportionately from intervention efforts designed to promote positive functioning. Just as importantly, such intervention work can determine whether, as presumed by differential-susceptibility thinking, allelic variants associated with resilience in the face of adversity lead carriers to benefit less – or not at all – from interventions designed to foster positive functioning.

Consideration of the notion that developmental plasticity be regarded as an individual-difference construct raises the issue of whether plasticity is domain general or domain specific. That is, are more malleable individuals especially responsive to and influenced by a wide variety of environmental conditions and developmental exposures and other individuals not particularly influenced by the same large set of experiences? Or are individuals mostly “mosaics” of plasticity, being highly sensitive to some contextual conditions but not others?

However surprising it might seem, there is some evidence for the domain general view. Consider the results of two interventions which used strikingly dissimilar methods to promote different aspects of development. In one case the intervention sought to foster sensitive parenting in order to reduce toddler’s externalizing behavior (9) and cortisol-related stress reactivity (10), whereas in the other a computerized instructional program was employed to foster preschooler’s phonemic awareness and, thereby, early literacy (11). Despite the dramatic differences in the interventions and in the features of development studied, it was children carrying 7-repeat DRD4 allele who benefited disproportionately, if not exclusively, from both. Before it can be concluded, however, that plasticity is more domain general than domain specific, far more work is required. We suspect that some individuals will be on the extremes of plasticity – highly responsive or virtually unaffected by almost all contextual conditions – but that most might fall somewhere between these extremes.

CONCLUSIONS

An evolutionary perspective led us not only to appreciate the costs as well as benefits of developmental plasticity but, as a result, why individuals should vary in their susceptibility to environmental influences. Moreover, this framework led us to expect – and find – that individuals long regarded as especially vulnerable to adversity due to their genetic make-up disproportionately benefit from supportive experiences – due to the very same genetic factors. This led to re-conceptualizing some presumed vulnerability genes as putative plasticity genes.

Despite the evidence summarized here and elsewhere (1,4), much still needs to be learned about when and why genetic factors operate as plasticity rather than just vulnerability factors. Nevertheless, the study of differential susceptibility to environmental influences has already highlighted both the benefits of considering human development from an evolutionary perspective and the drawbacks of focusing disproportionately on contextual risk, dysfunctional development and vulnerability – in that it makes it difficult to discover that the very genetic factors that might be related to dysfunction when individuals experience contextual adversity can also
be related to especially competent functioning when they encounter supportive developmental contexts.

**References**


DOI 10.1002/wps.20092