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SPECIAL SECTION EDITORIAL

What works for whom? Genetic moderation of intervention efficacy

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The big question in human development intervention, just like in modern medicine, is *What works for whom*? Although it is well appreciated that interventions do not succeed with all whom they reach, a common presumption as to why they often prove less effective than anticipated focuses on poor implementation. There can be no doubt that fidelity to program model matters greatly. Nevertheless, an expanding body of experimental-intervention research (e.g., Beach, Brody, Lei, & Philibert, 2010; Kegel, Bus, & van IJzendoorn, 2011), building directly on theory regarding differential susceptibility to environmental influences and observational evidence to this effect (Belsky, Bakermans-Kranenburg, & van IJzendoorn, 2007; Belsky & Pluess, 2009, 2013; Ellis, Boyce, Belsky, Bakermans-Kranenburg, & van IJzendoorn, 2011), makes it clear that characteristics of individuals involved in interventions matters as well when it comes to explaining "what works for whom." Answering the question of which individual characteristics matter holds the promise of enabling intervention programmers to tailor interventions to individuals, thereby improving the efficiency of program delivery and maximizing impact. The main goal of this Special Section of *Development and Psychopathology* is to share the latest experimental intervention research addressing this issue that focuses on the genetic makeup of individuals as determinants (or moderators) of variation in intervention efficacy.

The differential susceptibility model has important clinical and practical implications. The average effects of preventive or therapeutic interventions in human development are only modest, with effect sizes barely larger that Cohen's criterion for a weak effect ($d = 20$), reflecting the standardized difference between the control and intervention group on the core outcome the intervention is designed to impact. Failure to consider variation in susceptibility, however, means that such intervention effects may be much larger for more susceptible individuals and much smaller for the less susceptible (Belsky & Pluess, 2009, 2013; van IJzendoorn, Bakermans-Kranenburg, Belsky, et al., 2011). Weak intervention effects might be taken as a sign of a cul-de-sac, not only in research on intervention efficacy but also in terms of how well current thinking about developmental psychopathology (and human development enhancement) can inform efforts to prevent or remediate problematic functioning or enhance well-being. Policymakers and funding agencies might be less inclined to support efforts to document intervention efficacy or to roll out evidence-based interventions on a larger scale given concerns that impact might be limited and/or not cost effective. Being aware of differential susceptibility of participants in preventive or therapeutic interventions creates more realistic expectations of intervention efficacy while illuminating the hidden efficacy of interventions targeting groups composed of a mixture of both more and less susceptible individuals (Bakermans-Kranenburg & van IJzendoorn, in press). It is important to appreciate that a focus on genetically based differential susceptibility can raise ethical issues concerning stigma, discrimination, and equity of service provision (Ellis et al., 2011), but this should not lead to ignoring replicated evidence that some individuals are more open to environmentally induced change, for better and for worse, due to their genetic makeup.

Should it prove the case that genetic characteristics of individuals account for and perhaps even causally influence the efficacy of particular interventions, as multiple reports in this Special Section indicate, a second issue arises beyond "what works for whom." That involves the mechanisms accounting for why a particular intervention proves more effective for some than for others. Although some of the research

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to be reported in the Special Section will focus on traditional cognitive, emotional, and behavioral mechanisms, here we call attention to the potential role of epigenetic processes. There is increasing appreciation that experiences, including perhaps intervention-related ones, can affect gene expression and thereby cognitive, emotional, and behavioral functioning (Meaney, 2010; van IJzendoorn, Bakermans-Kranenburg, & Ebstein, 2011). Thus, in addition to heralding cutting-edge research identifying genotypic markers of intervention efficacy, when we planned this Special Section we expected to be in a position to include work devoted to epigenetic mediation in an effort to illuminate how intervention effects "get under the skin" and come to affect human development. Unfortunately, our editorial ambitions exceeded the evidence base. Thus, even though we can raise this issue of epigenetic mediation, and include one paper in the Special Section examining intervention effects on methylation in rodents (van der Doelen, Arnoldussen, Homberg & Kozicz, 2015 [this issue]), as well as a human observational study addressing the same general issue (Chen et al., 2015 [this issue]), while calling attention to prior studies documenting epigenetic mediation of intervention efficacy (Perroud et al., 2013; Roberts et al., 2014; Yehuda et al., 2013), additional evidence of the latter kind must await future empirical progress.

Given these introductory comments, in the remainder of this introductory essay, we delineate the theoretical and empirical foundations of the work that makes up the Special Section and provide overviews the papers that are included before drawing some general conclusions.

Theoretical Foundations: Differential Susceptibility to Environmental Influences

A differential-susceptibility perspective on environmental influences differs fundamentally from the traditional approach to conceptualizing Person × Environment interaction. Whereas the classic diathesis–stress framework focused on those most "vulnerable" to contextual adversity (e.g., poverty, maternal depression, and family conflict; Zuckerman, 1999), differential susceptibility highlights that those most likely to be adversely affected by some negative environmental exposure or developmental experience will be those most likely to benefit from contextual support and/or enrichment as well (Belsky, 1997, 2005; Belsky et al., 2007; Ellis et al., 2011). Numerous results from observational studies provide support for the latter proposition (for reviews, see Belsky & Pluess, 2011, 2013), highlighting, among other factors, the role of genotype in predicting for whom positive *and* negative experiences and exposures affect, respectively, positive *and* negative functioning and development.

Consider, in this regard, evidence documenting such for better *and* for worse results in the case of those carrying one or more serotonin transporter linked polymorphic region gene (*5-HTTLPR*) short alleles when the rearing predictor and child outcome were, respectively, maternal responsiveness and moral internalization (Kochanska, Kim, Barry, & Philibert, 2011), child maltreatment and antisocial behavior (Cicchetti, Rogosch, & Thibodeau, 2012), supportive parenting and positive affect (Hankin et al., 2011), and, in the case of African American adolescents, perceived racial discrimination and conduct problems (Brody et al., 2011). Consider, as well, evidence showing heightened (or exclusive) susceptibility of individuals carrying the dopamine receptor D4 gene (*DRD4*) seven-repeat (7R) allele when the environmental predictor and developmental outcome were, respectively, maternal positivity and prosocial behavior (Knafo, Israel, & Ebstein, 2011), early nonfamilial childcare and social competence (Belsky & Pluess, 2013), contextual stress/support and adolescent negative arousal (Beach et al., 2012), and childhood adversity and young-adult persistent alcohol dependence (Park, Sher, Todorov, & Heath, 2011). Of special importance perhaps is that two recent meta-analyses of children and/or adolescents reveal that those carrying certain dopamine genes, including *DRD4* 7R, prove to be more affected by positive and negative environmental exposures than do others (van IJzendoorn & Bakermans-Kranenburg, 2011), with the same being true, at least for Caucasian children, for those carrying *5-HTTLPR* short alleles (van IJzendoorn, Belsky, & Bakermans-Kranenburg, 2012).

Implications for Intervention

One of the major consequences of differential-susceptibility theorizing has been to direct attention toward variation in response to positive/supportive environmental influences, a focus that was neglected for many years due to the influence of diathesis–stress thinking, which highlighted variation in response to adversity only. It is of interest to note that whereas diathesis–stress research long focused on characteristics of individuals to explain their susceptibility to negative experiences and exposures, including genetic ones, only limited attention was paid to such factors when it came to illuminating variation in response to supportive experiences and exposures. Perhaps the best evidence of this is that most thinking about variation in intervention efficacy highlighted the importance of program implementation, with little if any attention paid to characteristics of program recipients (beyond perhaps demographic ones or preintervention levels of functioning).

As it turns out, there is ever-growing *experimental* evidence, which this Special Section expands and extends, that genetic factors matter when it comes to illuminating what works for whom. Recent genetically informed intervention evaluations indicate that alleles long presumed to place individuals at risk in the face of adversity (i.e., *5-HTTLPR* short and *DRD4* 7R) or to promote resilience (i.e., not short/not 7R) are associated with them being, respectively, susceptible or not to the benefits of intervention (for the first experimental genetic differential susceptibility evidence, see Bakermans-Kranenburg, van IJzendoorn, Pijlman, Mesman, & Juffer, 2008). Consider in this regard Drury et al.'s (2012) data showing that it was only the children growing up in Roma-

nian orphanages who carried *5-HTTLPR* short alleles who benefited from being randomly assigned to high-quality foster care, in terms of reductions in the display of indiscriminant friendliness (but for counterevidence in the case of an extended, intensive intervention with nonmoderated high effectiveness, see Cicchetti, Rogosch, & Toth, 2011). Eley et al. (2012) also documented intervention benefits restricted to short-allele carriers, although their design included only treated children. Turning to *DRD4*, Kegel et al. (2011) tested and found support for the hypothesis that it would be 7R carriers who would benefit from specially designed computer games promoting phonemic awareness and, thereby, early literacy. Other randomized-controlled trial results point in the same direction with regard to *DRD4* 7R, including research on African American teens in which substance use was the outcome examined (Beach et al., 2010; Brody, Chen, & Beach, in press; Brody et al., 2014). What makes these diverse results so interesting is that they concern not only quite diverse means of intervention (parent training, cognitive behavioral therapy, and computer-assisted learning) but also have as their targets prevention, remediation, and enhancement.

Special Section Papers

When it comes to this Special Section and research on genetic moderation of intervention efficacy, the papers included focus exclusively on randomized control trial experiments and genetic differential susceptibility. The main reason is that experiments have at least three distinct advantages compared to observational/correlational studies of Gene × Environment (G × E) interaction (van IJzendoorn & Bakermans-Kranenburg, 2015 [this issue]). First, the genetic marker of differential susceptibility cannot be correlated with the manipulated environment, because randomization implies independence of (change in) the environment and genetic makeup. This obviates any concern about gene–environment correlation accounting for a detected statistical G × E interaction, a problem that plagues virtually all observational G × E research. Second, many correlational G × E studies assess genes in a very precise way but fail to measure the environmental component in an equally precise manner. Experimental manipulation of the environment often reduces measurement error in the environment, as long as the intervention is done in a standardized way. Third, correlational G × E studies have been criticized for their lack of statistical power and risk of spurious findings (Duncan & Keller, 2011). Randomized G × E experiments have considerably more power, estimated by some to be equivalent to correlational studies with 10 times more subjects (for details, see Bakermans & van IJzendoorn, in press).

The first eight articles of this Special Section address the issue of whether intervention effects under consideration vary as a function of child genotype, usually with a priori expectations as to which children should benefit most as a result of their genetic makeup. Zöe Brett et al. do so when investigating how children with extensive exposure to severely depriving Romanian orphanages respond to being randomized to receive high-quality foster care (or not), focusing on externalizing behavior and the *5-HTTLPR* polymorphism. Dante Cicchetti, Sheree L. Toth, and Elizabeth D. Handley also focus on the serotonin transporter gene when evaluating whether the effect of interpersonal psychotherapy proves effective in preventing major depressive disorder in a sample of economically impoverished mothers of infants; but they extend Gene × Intervention (G × I) inquiry by also examining the moderating effect of genotypic variation in corticotropin releasing hormone receptor 1. The results prove interesting, even somewhat surprising, with respect to which genetic subgroup benefits the most, perhaps due to the racial composition of the sample, which was disproportionately African American or biracial.

In the third paper, Gene H. Brody, Tianyi Yu, and Steven R. H. Beach test the proposition that rural African American youth who are carriers of *DRD4* long alleles would benefit most from a family-oriented intervention targeting both parents and adolescents in order to prevent adolescent drug use. It is important that these investigators not only document genetic moderation of intervention efficacy but also address what they refer to as a "second-generation" question of G × I research by illuminating cognitive processes responsible for detected prevention effects in an effort to understand not just for whom the intervention proved effective but how its effect was instantiated. Of note, the aforementioned paper by Cicchetti et al. in this Special Section extends G × I work in exactly the same way, but with a focus on social rather than cognitive mediational processes. The work of H. Harrington Cleveland et al., which comes next, also focuses on *DRD4* as a genetic moderator, in this case of a multifaceted intervention designed to prevent underage alcohol use (measured in ninth grade) that was implemented in some 28 communities. This work chronicles genetic moderation of intervention efficacy that is itself dependent on level of maternal involvement when children were in sixth grade. In contrast to all the work just cited, the fifth paper, by Rachel D. Plak, Cornelia A. T. Kegel, and Adriana G. Bus, focuses on an intervention designed to enhance functioning, not just prevent problems. Thus, these investigators report that a computerized instructional program designed to promote text comprehension and thereby literacy proves effective, but only in the case of those carrying long *DRD4* alleles.

Not all papers included in the Special Section focus on "the usual suspects" of *DRD4* or *5-HTTLPR*. The sixth paper, by Dustin Albert et al., extends an earlier analysis of genetic moderation of the well-known Fast Track Prevention program. Having already reported that this multiple-year, multifaceted program, which began when children were in kindergarten, proved effective in preventing externalizing psychopathology at the age of 25 depending on the glucocorticoid receptor gene, this report addresses whether the genetically moderated prevention effect was evident much earlier in life and whether it mediated the effect detected later in life. In the seventh report, Joni Sasaki, Taraneh Mojaverian, and

Heejung J. Kim turn attention to the oxytocin receptor gene polymorphism, testing the proposition that GG homozygotes would prove especially sensitive to social conditions, which they evaluate in a social psychology experiment that attempts to foster self-control by means of religion priming. In the eighth paper, Rachelle J. Musci et al. move beyond a focus on single candidate-gene moderators to examine the moderational effect of a polygenic score. The results revealed that their composite moderator, based on more than 12,000 single nucleotide polymorphisms identified in prior tobacco-related research, moderated the effects of a school-based intervention implemented in kindergarten on age of first tobacco use.

The final three papers differ from those just highlighted, all of which present new evidence pertaining to genetic moderation of intervention efficacy. The contribution by Rick Van der Doelen et al. relies on a *rodent model* to examine intervention effects on epigenetic processes of methylation, a presumed mediator of the environmental manipulation on behavior. The paper by Li Chen et al., also examines, in the context of an *observational* study, how the brain-derived neurotropic factor moderates not only the effects of prenatal anxiety on gene expression but also the effects of such gene expression on the endophenotype of neonatal brain volume. As already noted, future work will hopefully extend research of this kind to determine, whether as presumed by these investigators, and many contributors to the Special Section, epigenetic processes are a critical pathway by which intervention effects become instantiated.

The final paper of the Special Section seeks to empirically examine and summarize emerging knowledge about the moderational effects of intervention effects when the focus is on perhaps the two most recent frequently used candidate genes in G × E and G × I research, *DRD4* and *5-HTTLPR*. Thus, Marinus H. van IJzendoorn and Marian L. Bakerman-Kranenburg report a meta-analysis of all existing G × I studies, whether prevention, remediation, or enhancement oriented, or resulting from social-psychological experiments like that of Sasaki et al., although not of pharmacological interventions. The results prove most interesting.

Conclusion

Because research on the genetic moderation of environmental influences, that is, G × E research, has exerted such a powerful effect on thinking about the interaction of nature and nurture since the publication of Caspi, Moffitt, and associates' (2002, 2003) papers on this subject, it is somewhat surprising that it has taken as long as it has for intervention-oriented investigators to address the core issue on which this Special Section is focused: whether intervention efficacy varies as a function of the target individual's genetic makeup. Although it is not entirely clear why that has been the case, we are most pleased to see the ever-growing interest in this important subject. We suspect that G × I research has lagged behind G × E research for two reasons. The first reason is that until the emergence of differential-susceptibility theorizing, there was an absence of consideration that some individuals might be more developmentally plastic, for better and for worse, than others, even though diathesis–stress thinking has long acknowledged that some are likely to be more vulnerable to adversity than others.

The second reason may have to do with the intellectual and ethical discomfort that some feel when considering the implications of differential-susceptibility thinking for intervention: if only some are likely to benefit from an intervention, whether prevention, remediation, or enhancement in character, should it only be provided to such individuals? Our experience teaches that some who value *equity* especially highly believe that the answer to this question is "no," whereas others who privilege *efficacy*, and cost effectiveness, regard the answer to this question as "yes." For several reasons we think both of these answers are premature, at least given the present state of our knowledge.

If research continues to reveal, as the meta-analysis by van IJzendoorn and Bakermans-Kranenburg in this Special Section begins to suggest, that we can identify those who do and do not benefit from many diverse interventions, then it would seem questionable to provide services that the community pays for but that are unlikely to prove effective simply so that everyone is treated, or seems to be treated, in the same way. At the same time, even if the evidence indicates that some do not benefit whereas others do from particular interventions, it does not follow that those who prove relatively unsusceptible will be unsusceptible to *any and all* interventions. It may just be the case, and this *must* be the working hypothesis: that they are simply unresponsive to the interventions being administered. If this is the case, the imperative would be to expand the duration, intensity, or range of interventions and thereby determine just how generally or specifically unsusceptible are those who appear not to benefit from interventions being implemented. As one reads the discussion sections of many of the papers included in the Special Section, it is clear that the view we are advocating is widely shared.

We are currently far from a point where we can claim that we should be providing interventions to some and not others due to their genetic makeup. With the current state of knowledge, genetic screening for differential susceptibility would invariably produce too many false negatives as well as false positives. Furthermore, every individual has the basic human right to grow up in good-enough rearing environments and to be enabled to contribute to society according to his or her potentials. This is why we have a system of basic education that promotes literacy and numeracy without wanting to leave any child behind. As another example of the same principle, even though some children with a specific genetic makeup seem more vulnerable to the detrimental effects of institutional care whereas others seem relatively immune to many of these (Brett et al., 2015 [this issue]; Nelson, Fox, & Zeanah, 2014), institutional care reflects structural neglect; as such, it qualifies as lower quality care than any child deserves. All children, according to United Nations Convention on the Rights of the Child (1989), are entitled to (foster or adoptive) family-

based care. In other words, just because care that is regarded as neglectful, or worse, may not adversely affect a child in a measurable manner, this is is not a basis for regarding it as sufficient or acceptable.

These comments notwithstanding, we are clearly in a position where we should be asking, based on differential-susceptibility theorizing and the evidence presented in this Special Section and elsewhere, whether some are more likely to benefit from intervention than others because of their genetic makeup (and/or other personal characteristics, like temperament and stress physiology) and, if so, just how broadly susceptible or not are individuals who vary in the benefit they derive from particular interventions. It is in the spirit of such understanding that we are most excited about the work presented in this Special Section and its implications for future preventive and therapeutic intervention research.

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