Prenatal Smoking and Attention-Deficit/Hyperactivity Disorder: DRD4-7R as a Plasticity Gene

To the Editor:

Virtually all gene × environment interaction (GxE) research in the field of psychiatric genetics is guided by the diathesis-stress model, which stipulates that certain individuals, for genetic reasons (i.e., the diathesis), will be most likely to develop psychopathology in the face of some identified adversity (e.g., child maltreatment, negative life events), whereas others, lacking the diathesis, will fail to do so or be substantially less likely to do so, even under the very same stressful conditions (1–3). And, to date, any number of studies have been published, many with replicated findings (e.g., 4–7), proving consistent with this prevailing conceptual framework. Recently, and seemingly in line with diathesis-stress thinking, Neuman et al. (8) reported that the anticipated adverse effects of prenatal smoking on attention-deficit/hyperactivity disorder (ADHD) were more pronounced in children carrying the seven-repeat (7R) allele of the dopamine receptor D4 (DRD4) gene.

What was not recognized in the Neuman et al. (8) data and thus not highlighted in their Biological Psychiatry article, however, was that the very same genotype that emerged as most vulnerable to the adverse effects of prenatal smoking vis-à-vis ADHD also proved least likely to show signs of ADHD when its carriers were not exposed to prenatal smoking. Figure 1, based on unpublished data provided by Neuman, graphically displays this pattern of results. The data presented show, consistent with Belsky’s (9,10) differential-susceptibility hypothesis, that children carrying the putatively “at-risk” allele (i.e., DRD4-7R) were not only those most likely to be diagnosed with any kind of DSM-IV ADHD diagnosis when exposed to prenatal smoking, just as a diathesis-stress model would predict, but also functioned best, at least in terms of being least likely to be so diagnosed, when exposed to a positive or at least benign intrauterine environment (i.e., no prenatal smoking). In other words, and consistent with differential-susceptibility thinking, children vary—as a function of their genotype—in their developmental plasticity in a for-better-and-for-worse manner (11).

The fact that those most likely to be adversely affected by a problematic environment are also most likely to benefit from a supportive one suggests that the DRD4-7R allele, often conceptualized as a “vulnerability gene,” might be better regarded as a “plasticity gene” (12). No doubt Neuman et al. (8) missed the result in their data to which we are calling attention—and that close scrutiny of their Table 5 reveals (given that the odds ratios for the nonexposed DRD4-7R group are less than 1.0)—because the conceptual framework guiding their psychiatric genetic work simply did not entertain, much less anticipate, this possibility.

As it turns out, the past few years have produced numerous GxE findings in line with differential susceptibility, ones that are often missed and, like Neuman et al. (8), interpreted in terms of diathesis-stress. An abbreviated, but nevertheless extensive, review of relevant findings can be found in Belsky et al. (13), with a more thorough summary of differential-susceptibility evidence in both GxE and temperament × parenting research under review (J.B. and M.P., unpublished data, February 2009).

Meriting appreciation is that this letter documents for the first time GxE results consistent with differential-susceptibility thinking that involves the prenatal environment, as all others studies providing such evidence, including ones involving DRD4-7R, concern the postnatal environment, whether in childhood or adulthood.

Figure 1. Percentage of children diagnosed with ADHD (DSM-IV) by genotype and exposure to maternal prenatal smoking (without any covariate adjustments). ADHD, attention-deficit/hyperactivity disorder.

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