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Enhancing the Gene-Environment Interaction Framework Through a Quasi-Experimental Research Design: Evidence from Differential Responses to September 11

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Abstract

This article uses a gene-environment interaction framework to examine the differential responses to an objective external stressor based on genetic variation in the production of depressive symptoms. This article advances the literature by utilizing a quasi-experimental environmental exposure design, as well as a regression discontinuity design, to control for seasonal trends, which limit the potential for gene-environment correlation and allow stronger causal claims. Replications are attempted for two prominent genes (5-HTT and MAOA), and three additional genes are explored (DRD2, DRD4, and DAT1). This article provides evidence of a main effect of 9/11 on reports of feelings of sadness and fails to replicate a common finding of interaction using 5-HTT but does show support for interaction with MAOA in men. It also provides new evidence that variation in the DRD4 gene modifies an individual's response to the exposure, with individuals with no 7-repeats found to have a muted response

Introduction

Social and medical scientists have often sought to uncover the determining factors of important economic, social, and health-related outcomes. In particular, many researchers have focused on the heterogeneity in responses to a common cause—for example, poor health. Why is it that some individuals are resilient to environmental insults while others experience significant reductions in life outcomes? One potential source of this variation relates to genetic vulnerabilities and predispositions that may interact with environmental exposures. Indeed, gene-environment interaction ($G \times E$) has been implicated in explanations of heterogeneity in response to medical treatments for depressive symptoms, among others, as well as differential responses to a host of environmental stressors and exposures (Uhr et al. 2008; Ising et al. 2009; see also Kato and Serretti [2010] for a review). Specifically, in two landmark studies, a functional polymorphism in the *MAOA* gene was shown to moderate individuals' response to childhood maltreatment in the development of antisocial behaviors (Caspi et al. 2002), and a functional polymorphism in the *5-HTT* gene

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was shown to moderate response to stressful life events in predicting depressive outcomes (Caspi et al. 2003). These findings have been controversial and have spawned multiple attempts at replication and extension. Indeed, there are now competing meta-analyses, but although some suggest that the results are not robust across studies (Risch et al. 2009; Munafò et al. 2009), the latest analysis suggests that they are (Karg et al. 2011).

While the idea of $G \times E$ is persuasive, empirically examining this phenomenon has been hampered by both data and methodological issues. A growing number of researchers have called attention to the importance and ubiquity of gene-environment correlations (rGE) in these analyses, which could mask true causal effects as well as produce evidence of $G \times E$ when the true effects are in fact gene-gene interactions (Jaffee and Price 2007; Conley 2009). More generally, the use of nonexperimental variation in environmental exposures in most research using this framework limits researchers' ability to make causal claims. In order to reduce the importance of rGE in the $G \times E$ framework and strengthen the ability to make causal inferences, then, researchers have sought to focus on experimental or quasi-experimental environmental influences, though this focus is only now emerging in the literature (Conley and Rauscher 2010; Fletcher 2012).

In order to circumvent these issues, more robust empirical specifications and the use of quasi-experimental variation in environmental exposures ("E") are needed. This article moves in this direction by utilizing the coincidental survey window of data collection from a national survey taken in the days surrounding the 9/11 terrorist attacks, combined with the molecular DNA information now available in this survey, to examine differential responses to the attacks by genotype. The effects of the terrorist attacks on mental health (Galea et al. 2002; Schlenger et al. 2002; Schuster et al. 2001; Silver et al. 2002) and other outcomes, such as in the labor market (Knudsen et al. 2005), have been extensively documented; see Mardikian (2008) for a review of the literature. Additionally, research has shown important heterogeneity in individuals' responses, for example, based on prior mental health (Calderoni et al. 2006).

Using the same dataset as that employed by the current article, researchers have provided evidence of large increases in depressive symptoms, particularly reports of sadness, following the attacks, which then returned to baseline levels within about two months (Ford et al. 2003). One limitation of this type of research is the use of a pre-post analysis, since depressive symptoms have a strong seasonal pattern. Thus, alternative and more precise methods may be required to estimate causal effects.

Methodologically, in addition to using a quasi-experimental research design, this article contributes to the literature by incorporating a regression discontinuity design into a standard $G \times E$ analysis. This study also focuses on a particular developmental period, as all study participants were between 18 and 26 years old, and allows the use of a measure of an external stress that is objective rather than self-reported. These strengths, combined with the quasi-experimental exposure, allow much stronger causal claims than those permitted by the extant literature and could point the way toward new directions in examining gene-environment interaction effects in human populations.

Data and Methods

The data for this study were drawn from Wave 3 of the National Longitudinal Study of Adolescent Health (Add Health). Add Health was a U.S. school-based longitudinal study of a nationally representative sample of individuals who were in grades 7 through 12 in 1994–95. The respondents were resurveyed in 1996 (Wave 2), 2001–02 (Wave 3), and 2007–08 (Wave 4). Generally, this large national survey was carried out to explore the influences of individual attributes and environmental factors in determining health and health-related behaviors. Key details are available elsewhere (Harris 2009; Harris et al. 2009) and in the data appendix.

The Wave 3 data collection coincidentally covered the months before and after the terrorist attacks of September 2001 and included several measures of poor mental health, including the nine-item short form of the Center for Epidemiologic Studies Depression (CES-D) Scale (Roberts, Lewinsohn, and Seeley 1991). Indeed, researchers (Ford et al. 2003) have used these data to show evidence of a short-lived main effect of being interviewed shortly after 9/11 in comparison to shortly before 9/11 in predicting elevated depressive symptoms—with a large and statistically significant effect of reports of sadness. In particular, Ford and colleagues used a self-report of how often it was true that an individual “w[as] sad during the past seven days,” with responses including (a) never or rarely, (b) sometimes, (c) a lot of the time, and (d) most of the time or all of the time. In the present study, I followed Ford and colleagues to focus on the main effect of the 9/11 attacks on this sadness variable (and not other measures of depressive symptoms) and created a binary indicator of whether the respondent reported being sad “a lot” or “most/all” of the time.

In addition to the self-reported demographic and health data, the Wave 3 data collection included biological (saliva) samples from a subset of approximately 2,300 individuals who have since been genotyped for five polymorphisms in genes in the dopaminergic and serotonin systems—*5-HTT*, *MAOA*, *DRD2*, *DRD4*, *DAT1*—that have been shown to modulate the stress response in prior studies (see Harris et al. [2006] for details). While genome-wide association study (GWAS) data for this sample are forthcoming, the limited availability of genotypic data allows only a limited number of tests to be examined. See Table 1 for the list of polymorphisms and distributions and summary statistics for the sample and Appendix Table 1 for a comparison of the full Add Health sample and the sample assessed for genotypic data (the “analysis sample”).

Approximately 10 percent of the sample had depressive symptom scores over 10, with the scale’s average score being 4.8 (Khan et al. [2009], among others, have used this cut point for these data). Importantly, the same individuals had also been administered a depression scale during Wave 1 (seven years prior), so the analysis is able to show that individuals with higher previous depressive symptoms were not more likely to be interviewed following 9/11. Thus, the exposure (interview date) is uncorrelated with prior depressive symptoms. The table also separates the specific depression scale measures and shows the proportion of individuals who reported the symptom at least “a lot” of the time. For example, 9 percent reported they had felt sad a lot of the time in the past week. Because very few individuals were interviewed in July and early August 2001, almost 60 percent of the analysis sample

interviewed in a 120-day window around 9/11 was interviewed after the event. This subsample of the data was the key analysis sample used in this study.

In order to examine whether there is evidence of a gene-environment interaction in determining elevated depressive symptoms in response to stress, this study used a standard framework to detect $G \times E$ but also extended the methodology to incorporate a regression discontinuity design. The quasi-experimental timing of the interview (with respect to genotype; see Table 2) allowed a straightforward use of a linear probability model:

$$depression = \beta_0 + \beta_1 Gene + \beta_2 Post9/11 + \beta_3 GeneXPost9/11 + \beta_4 X + \varepsilon$$

where *Gene* is the polymorphism of interest; *Post9/11* is an indicator variable reflecting whether the interview day was before (0) or after (1) the terrorist attacks; *X* is a vector of individual demographic characteristics (sex, race/ethnicity, age); and β_3 is the coefficient of interest, the coefficient reflecting the interaction between a genotype and the environmental exposure. The *Gene* variables are coded as follows (see also Table 1 notes): *5-HTT* includes an indicator variable for Short/Short, with individuals who are Short/Long or Long/Long as the omitted category; *MAOA* includes an indicator for individuals with zero 3-repeats, with the omitted category including individuals with one or two 3-repeats; *DRD4* includes an indicator for individuals with zero 7-repeats, with the omitted category including individuals with one or two 7-repeats; *DRD2* includes an indicator for individuals with the A2 allele, with the omitted category including individuals with the A2/A1 allele or the A1 allele; and *DAT1* includes an indicator for individuals with either one or two 10-repeats, with individuals with zero 10-repeats as the omitted category.

There could be some concern that the pre-post analysis of previous research (Ford et al. 2003) was potentially confounded with the well-known seasonal patterns relating to depressive symptoms, particularly seasonal affective disorder, which peaks in the fall and winter months (Tefft 2012), all of which of course followed 9/11. Therefore, in order to tighten the comparison groups and reduce the importance of seasonal patterns, this study incorporated a regression discontinuity (RD) design into the basic framework:

$$depression = \beta_0 + \beta_1 Gene + \beta_2 Post9/11 + \beta_3 GeneXPost9/11 + \beta_4 X + \beta_5 f(\text{interview day}) + \varepsilon$$

where *f* is a flexible function of the so-called “running variable,” which in this case is the exact date of an interview in relation to 9/11 (Thistlethwaite and Campbell 1960; Imbens and Lemieux 2008). The idea is that individuals interviewed shortly before and after 9/11 were similar in the observable and unobservable predictors of depression.

Generally, RD designs are used for evaluating the causal effects of a treatment or intervention when assignment to a treatment status is determined (at least in part) by whether the value of an observed covariate lies on one side of a fixed threshold (Imbens and Lemieux 2008). This covariate is called the *running variable* and may be associated with the outcome of interest, but the association is assumed to be smooth, with the implication that any discontinuity in the conditional distribution of the outcome as a function of this

covariate at the threshold is interpreted as evidence of a causal effect of treatment status. There are two classes of RD designs: sharp and fuzzy. In sharp RD designs, treatment status is a deterministic function of a covariate, where the probability of treatment status changes from 0 to 1 at the threshold. In comparison, in fuzzy RD designs, the probability of treatment status increases at the threshold, but not necessarily from 0 to 1. This study used the sharp RD design. The main assumption underlying the RD design is that the covariates are smooth throughout the threshold, so that any discontinuity in the outcome is caused by the change in treatment status and not by other confounding influences. In order to verify that this assumption is met, the typical approach is to empirically test whether a set of covariates is indeed smooth at the threshold or whether there is any “bunching” at the threshold (Imbens and Lemieux 2008). For example, in the case of interviews conducted following 9/11, it could be that individuals interviewed following the event (those who were “treated”) had different characteristics than those interviewed before the event.

In order to check the assumptions of the RD design, Table 2 shows that individual characteristics (and genotypic variation) are “smooth” through the discontinuity—in this case, a binary indicator of whether the interview was conducted following 9/11. The results show no changes in observables around this cutoff for the genetic variation and several demographic characteristics, including age, gender, race, maternal education, and family income (as measured during high school, seven years prior). Likewise, Appendix Figure 1 plots the number of individuals who were interviewed in 10-day increments to show that there is no evidence of differential likelihood of response to the interview request—and no “bunching” of responses. Both Table 2 and Appendix Figure 1 strongly suggest that the RD design assumptions are met.¹ With these preliminaries concluded, I then investigated whether there was evidence in the data of gene-environment interaction in response to interview date.

Gene-Environment Interaction Results

Since not all individuals in the sample were genotyped, Appendix Table 2 replicates the findings for both the full sample (Ford et al. 2003) of Add Health respondents interviewed within a 120-day window surrounding 9/11 and the DNA sample, and shows that these sample changes do not affect the main results. In particular, individuals interviewed following 9/11 had higher rates of reported depressive symptoms, especially sadness. Figure 1 plots the findings for sadness, which suggest a quick peak in reports of sadness followed by a rapid return to baseline levels. Recall that the outcome is a binary variable of whether the respondent reported being sad “a lot” or “most of the time or all of the time” in the seven days before the interview (compared with reporting “never/rarely” or “sometimes”). Generally, these effects on depressive symptoms are quite localized to specific symptoms, some of which are likely not related to the specific stressor of 9/11. For example, Appendix Table 3 shows no effects of reports of “feeling that people disliked you” or reports of “trouble keeping your mind on what you were doing” but shows some effects on reports of

¹Additional results (available upon request) also show that controls for Wave 1 sadness do not alter the results of this study and are consistent with the findings in Table 2 that the “treatment” of being interviewed prior post-9/11 is exogenous. I thank an anonymous reviewer for the suggested analyses.

“being bothered by things.” Overall, the analysis shows no effects on meeting specific cutoffs for depression (e.g., a score of 9 or above on the CESD scale) (see Khan et al. [2009] for a discussion and validation of the use of this threshold for these data). Importantly, the results also suggest that prior depressive symptoms (as collected in 1994–95, during high school) are unrelated to 9/11—if anything, the negative coefficient suggests that the main findings for Wave 3 depressive symptoms could be slightly underestimated.

With these preliminaries outlined, Table 3 examines potential interaction effects between the five polymorphisms and stress in producing reports of sadness. The first two columns attempt to replicate prior results by examining the effect of being interviewed after 9/11 on the likelihood of reporting feelings of sadness “a lot” or “most/all” of the time during the prior week. Column 1 shows no evidence of interaction between the polymorphism in the *5-HTT* gene and stress, failing to replicate past research that used nonexperimental variation in stress (Caspi et al. 2003). Column 2 uses the sample of men with the *MAOA* polymorphism (following prior work, such as Caspi et al. [2002]) and shows evidence of a differential response to the stress of 9/11 based on genotype, with individuals with the low-density polymorphism appearing to be at an increased risk for reporting experiencing sadness following the stressful event, a finding that is consistent with prior research (Caspi et al. 2002).

Columns 3 through 5 examine whether there is any evidence of gene-environment interactions for three polymorphisms that have been the subject of less research (*DRD4*, *DRD2*, and *DAT1*). While the *DRD2* and *DAT1* genes show no statistically significant evidence of interaction with stress, there is evidence of such interaction for the polymorphism in *DRD4* (see Column 3). Specifically, for individuals with zero 7-repeat variants of the *DRD4* gene, the increase in sadness is only half the size as the increase for individuals with one or two 7-repeat variants of the gene, suggesting a large protective effect. Since this result is novel, additional analyses were undertaken to assess its robustness.

Table 4 shows that the results are insensitive to including basic demographic covariates or changes in the specification. Because there are some racial differences in the distribution of this polymorphism, the results are stratified in Columns 5 through 9 by race and gender; however, all results are robust, though less precisely estimated as a result of the smaller sample sizes.²

Figure 2 provides graphical evidence of the effects. The results are suggestive that the main effect of genotype for the *DRD4* polymorphism was to reduce the speed at which individuals returned to normal levels of depressive symptoms rather than to change the initial response to the 9/11 stressor.³

²Based on a reviewer comment, I also examined adding a race $\times$ 9/11 set of interactions as an additional test of robustness for population stratification. The results were unchanged and are available upon request from the author. I thank the anonymous reviewer for the comment.

³In order to examine the specificity of the protective effects, I also examined reports of trust in government. This was motivated by the results of previous research with the Add Health sample (Ford et al. 2003), which found that only sadness and trust in government appeared to be measurably affected by 9/11. Unlike the results for sadness, the results of this study suggest no genetic interactions in producing feelings of trust in government following the terrorist attack. This evidence is suggestive of localized genetic interaction effects specific to the stress response in producing higher depressive symptoms. Results available upon request.

Discussion

This study used a gene-environment interaction framework to examine the differential responses to an external stress based on variations in five genetic polymorphisms, including two attempts at replication and three examinations of novel interactions. While there has been much research on this general topic, this article advances the literature by utilizing quasi-experimental variation in the environmental exposure (whether a respondent was interviewed before or after 9/11), as well as a regression discontinuity design to control for seasonal trends. This article shows that since interview timing is unrelated to genotype, the “E” appears to be quasi-experimental, which limits potential rGE in this application. Furthermore, this study did not rely on self-reports of stress and limited its analysis to a sample of individuals at the same developmental stage, which further enhanced the research design (Monroe and Reid 2008). As in previous research on this topic and past work with these data (Ford et al. 2003), this study provides evidence of a main effect of 9/11 on reports of depressive symptoms, specifically feelings of sadness experienced shortly after the exposure. Sadness levels spiked immediately following the terrorist attacks and then rapidly returned to pre-attack levels within two months.⁴

This study has several limitations that should be considered when evaluating its findings. First, this study used the available data collection opportunistically in that the survey was not carried out in order to evaluate the effects of the 9/11 attacks on outcomes. Relatedly, the focus on the use of a specific external stressor (the 9/11 attacks) may not generalize to many other measures of exposure to stressors, nor to other age groups. Second, in addition to the potential limited generalizability of the 9/11 stressor for other measures of stress, it is also the case that the effects of the exposure likely differed based on many factors, including physical proximity to New York City, which were not measured in this study. The estimates in these data are therefore the average effect for the national population. Third, the available number of polymorphisms used in this study was small (five), limiting the ability to explore novel effects. Fourth, this study’s focus on a specific depressive symptom (sadness) rather than alternative clinically relevant mental health measures limited its attempts to replicate prior findings in the literature and also limits the general public health significance of the finding. This focus took the strategy of leveraging a finding of a main effect in the extant literature (Ford et al. 2003) in order to focus on a particular genotypic interaction rather than test all potential interactive effects for all depressive symptoms with all available genetic variations that have not been shown to be affected by this exposure. Fifth, because several of the findings were based on exploratory analysis, the precise mechanisms underlying the results for *DRD4* are currently not fully known.

The results suggest no detectable interaction between the exposure and the *5-HTT* polymorphism, which is contrary to findings reported in the literature using nonexperimental measures of stressful exposures (Caspi et al. 2003). This finding may be explained by the focus on a particular depressive symptom (sadness) rather than the more general measures

⁴Future work might reconsider $G \times E$ effects on phenotypes for which a main effect has not previously been found. Anxiety symptoms might be a natural direction but were not well measured in Wave 3 of the Add Health data. Other coping mechanisms, like tobacco or alcohol use, may also be an interesting direction for future inquiry to further elucidate pathways between stress and outcomes of interest, as moderated by genotype.

used in other research, it could suggest that the previously found interactions with *5-HTT* may be evident in some types of stressors but not all stressors (e.g., the terrorist attacks), or it could indicate that the findings of previous studies that did not use quasi-experimental designs may be spurious. However, the results suggest some evidence that the *MAOA* gene moderates exposure to stress for men, which is consistent with the findings of several other studies (Caspi et al. 2002; Jabbi et al. 2007; Kim-Cohen et al. 2006). This article thus provides new evidence that variation in the *DRD4* gene modifies an individual's response to the exposure, with individuals with no 7-repeats found to have a muted response—approximately 50 percent of the size of the effect for individuals with either a one or two 7-repeat genotype. Earlier evidence has suggested that individuals with the longer 7-repeat version of *DRD4* are more likely to report being exploratory and excitable (Ebstein et al. 1996), but this finding is mixed (Munafò et al. 2008). This link is consistent with the findings from this analysis, though additional analyses are needed to replicate these results and explore additional genes.

Graphical analysis suggests that the protective effects of the genotype seem to be based on the more rapid return to pre-attack sadness levels rather than on shielding the immediate effects. Results also suggest that this interaction with genotype is focused on measures of depressive symptoms and not on other outcomes that were affected by the terrorist attacks, such as increases in trust in government. These findings extend both the methods and measurement of environmental exposure to stress in the literature using a gene-environment interaction framework and suggest important specific interactive effects. Overall, this evidence suggests that genetic endowments are an important source of variation in responses to a stressful event in terms of the production of certain depressive symptoms in young adults. It also outlines a research direction that should benefit $G \times E$ research in the future by focusing on the use of quasi-experimental variation in “E” so that concerns with gene-environment correlation are reduced.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Proportion of individuals reporting “a lot” of sadness for each 10-day period around 9/11. Diamonds represent cell means at the 10-day level of aggregation and lines plot a Lowess smoother through the points, allowing for separate plots before and after 9/11. The increase in reports of sadness immediately following the 9/11 attacks is indicated by point 0 on the vertical axis. The vertical axis is measured in days before (negative values) or days after (positive values) September 11, 2001. The horizontal axis reports the proportion of individuals reporting a lot of sadness in the prior week. Each point aggregates individual responses in 10-day intervals based on the date of the survey administration.

Figure 2.

Proportion of individuals reporting “a lot” of sadness for each 10-day period around 9/11, results stratified by genotype. Diamonds represent cell means at the 10-day level of aggregation and lines plot a Lowess smoother through the points, allowing for separate plots before and after 9/11. No *DRD4* category: zero 7-repeats; alternative category: one or two 7-repeats. The increase in reports of sadness immediately following the 9/11 attacks is indicated by point 0 on the vertical axis. The vertical axis is measured in days before (negative values) or days after (positive values) September 11, 2001. The horizontal axis reports the proportion of individuals reporting a lot of sadness in the prior week. Each point aggregates individual responses in 10-day intervals based on the date of the survey administration.

Table 1

Descriptive statistics, Add Health individuals interviewed surrounding 120-day window of September 11, 2001, with genotypic data

Variable	Wave	Obs	Mean	SD	Min	Max
Depressed	3	1,439	0.10		0	1
Depression scale (9-item)	3	1,439	4.78	4.13	0	24
Depression scale (19-item)	1	1,435	11.42	7.62	0	50
Bothered by things (a lot) [Bother]	3	1,441	0.09		0	1
Could not shake the blues (a lot) [Blues]	3	1,441	0.07		0	1
Felt as good as other people (a lot) [As Good]	3	1,441	0.22		0	1
Trouble keeping your mind on what you were doing (a lot) [Mind]	3	1,441	0.11		0	1
Felt depressed (a lot) [Felt Depressed]	3	1,441	0.06		0	1
Felt too tired to do things (a lot) [Tired]	3	1,442	0.12		0	1
Enjoyed life (a lot) [Enjoyed]	3	1,442	0.17		0	1
Felt sad (a lot) [Sad]	3	1,440	0.09		0	1
Felt people disliked you (a lot) [People]	3	1,440	0.03		0	1
Trust federal government (scale)	3	1,435	0.32	0.96	-2	2
Trust federal government (strongly agree)	3	1,435	0.08		0	1
Trust federal government (agree)	3	1,435	0.37		0	1
Trust federal government (neither)	3	1,435	0.37		0	1
Trust federal government (disagree)	3	1,435	0.12		0	1
Trust federal government (strongly disagree)	3	1,435	0.05		0	1
Male	All	1,442	0.46		0	1
Age	3	1,442	21.82	1.68	18	26
Black	All	1,442	0.17		0	1
Hispanic	All	1,442	0.13		0	1
Asian	All	1,442	0.09		0	1
Indian	All	1,440	0.03		0	1
Other race	All	1,440	0.13		0	1
Centered interview day	3	1,442	9.24	26.90	-40	59
Interviewed after 9/11	3	1,442	0.58		0	1
A1A1 (low density) DRD2	All	1,440	0.08		0	1
A2A2 (high density) DRD2	All	1,440	0.53		0	1
Heterozygous DRD2	All	1,440	0.39		0	1
SS for 5-HTT	All	1,440	0.20		0	1
SL for 5-HTT	All	1,440	0.46		0	1
LL for 5-HTT	All	1,440	0.33		0	1
Zero 10-repeats of <i>DAT 1</i>	All	1,442	0.05		0	1
One 10-repeat of <i>DAT 1</i>	All	1,442	0.34		0	1
Two 10-repeats of <i>DAT1</i>	All	1,442	0.61		0	1
Zero 3-repeats of <i>MAOA</i> **	All	1,429	0.49		0	1
One 3-repeats of <i>MAOA</i> **	All	1,429	0.24		0	1

Variable	Wave	Obs	Mean	SD	Min	Max
Two 3-repeats of <i>MAOA</i> **	All	1,429	0.28		0	1
Zero 7-repeats of <i>DRD4</i> ***	All	1,442	0.64		0	1
One 7-repeats of <i>DRD4</i> ***	All	1,438	0.32		0	1
Two 7-repeats of <i>DRD4</i> ***	All	1,438	0.04		0	1

Notes:

* 10-repeats of *DAT1* includes 11-repeats and excludes 9-repeats.

** 3-repeats of *MAOA* includes 2-repeats and 3.5-repeats as “low activity” (Caspi et al. 2002).

*** 7-repeats of *DRD4* includes 8-repeats, 9-repeats, and 10-repeats and excludes all other repeats.

Table 2
Association between interview date and genetic and demographic characteristics, regression discontinuity evidence

Outcome	Zero 3-repeats <i>MAOA</i>	Long 5- <i>HTT</i>	Zero 7-repeats <i>DRD4</i>	<i>AI</i> 1 of <i>DRD2</i>	Zero 10-repeats, <i>DAT1</i>	Age	Male	Black	Hispanic	Mothers' education	Family income
Post 9/11	−0.002 (0.044)	−0.040 (0.046)	0.008 (0.047)	0.018 (0.026)	0.021 (0.021)	0.254 (0.163)	−0.004 (0.048)	0.012 (0.037)	−0.004 (0.033)	0.073 (0.242)	−2.283 (4.334)
Centered interview day	−0.000 (0.001)	0.000 (0.001)	0.001 (0.001)	−0.001 (0.000)	−0.001 ** (0.000)	−0.001 (0.003)	0.001 (0.001)	−0.001 (0.001)	−0.000 (0.001)	0.005 (0.004)	0.047 (0.078)
Constant	0.278 *** (0.023)	0.354 *** (0.024)	0.624 *** (0.025)	0.073 *** (0.014)	0.046 *** (0.011)	21.677 *** (0.086)	0.453 *** (0.026)	0.172 *** (0.019)	0.136 *** (0.017)	13.125 *** (0.128)	47.256 *** (2.320)
Observations	1,429	1,440	1,442	1,440	1,442	1,442	1,442	1,442	1,442	1,308	1,131
<i>R</i> ²	0.000	0.001	0.005	0.001	0.006						
<i>t</i> test statistic	.045	.870	.170	.692	.998	.005	.002	.002	.001	.004	.000

Notes: Robust standard errors clustered on the interview data presented.

*** *p* < .01;
** *p* < .05;
* *p* < .1. Insignificant coefficient for Post 9/11 suggests the sample characteristics do not change before compared to after the environmental exposure.

Table 3
Gene-environment effects of exposure to 9/11 on reports of “a lot” of sadness, evidence using five genes

Outcome	Sad Full	Sad Full	Sad Full	Sad Full	Sad Full
Sample					
Specification					
Gene					
Post 9/11 indicator	0.084*** (0.029)	0.067* (0.041)	0.130*** (0.034)	0.024 (0.059)	0.032 (0.072)
Gene	0.027 (0.030)	-0.037 (0.032)	0.026 (0.024)	-0.037 (0.044)	-0.137*** (0.052)
Gene × 9/11 indicator	0.008 (0.039)	0.072* (0.041)	-0.071** (0.032)	-0.036 (0.045)	0.079 (0.073)
Gene				0.066 (0.059)	-0.115** (0.050)
Gene × 9/11 indicator				0.080 (0.060)	0.041 (0.071)
Interview Date	-0.001** (0.001)	-0.002*** (0.001)	-0.001** (0.001)	-0.001** (0.001)	-0.001* (0.001)
Constant	0.046*** (0.016)	0.044* (0.024)	0.037* (0.021)	0.084*** (0.042)	0.168*** (0.048)
Observations	1,438	653	1,440	1,438	1,440
R ²	.009	.016	.011	.009	.014

Notes:

 $p < .01$;

**
 $p < .05$;

*
 $p < .1$. Beta coefficients and robust standard errors clustered on the interview data presented. Genes: *5-HTT* (SS Indicator; SL1LL omitted category); *MAOA* (zero 2-Repeats indicator; one or two 2-repeats omitted category); *DRD4* (zero 7-repeats indicator; one or two 7-repeats omitted category); *DRD2* (A2 allele, A2/A1 allele indicators; A1 allele omitted category); *DAT1* (one 10-repeat and two 1-repeat indicators; zero 10-repeats omitted category).

Table 4

The effects of 9/11 on depressive symptoms: Gene-environment interactions, full analysis sample and stratified by gender and race

Outcome	Sad	Sad	Sad	Sad	Sad	Sad	Sad	Sad	Sad	Sad	Sad	Sad	Sad
Sample	Full	Full	Full	Full	Male	Female	Black	Hispanic	White				
Specification	Basic	Xs	Quadratic	Xs	Xs	Xs	Xs	Xs	Xs				
Post 9/11 indicator	0.130 *** (0.034)	0.130 *** (0.034)	0.109 *** (0.037)	0.148 *** (0.045)	0.109 ** (0.051)	0.101 (0.089)	0.154 (0.094)	0.127 *** (0.044)					
Zero 7-repeats, <i>DRD4</i> genotype	0.026 (0.024)	0.030 (0.024)	0.030 (0.024)	0.042 (0.033)	0.016 (0.035)	-0.026 (0.058)	0.083 (0.068)	0.048 (0.032)					
<i>DRD4</i> genotype × 9/11 indicator	-0.071 ** (0.032)	-0.070 ** (0.032)	-0.069 ** (0.032)	-0.067 (0.043)	-0.063 (0.047)	-0.100 (0.079)	-0.082 (0.093)	-0.070 * (0.042)					
Interview date	-0.001 ** (0.001)	-0.001 ** (0.001)	-0.000 (0.001)	-0.002 *** (0.001)	-0.000 (0.001)	0.001 (0.001)	-0.003 *** (0.002)	-0.001 (0.001)					
Male		-0.040 *** (0.015)	-0.040 *** (0.015)				-0.029 (0.039)	-0.049 ** (0.020)					
Black		0.010 (0.021)	0.012 (0.021)	0.017 (0.028)	0.005 (0.030)								
Hispanic		-0.011 (0.058)	-0.013 (0.058)	0.041 (0.068)	-0.052 (0.099)								
Interview date squared			-0.000 (0.000)										
Interview date × post 9/11													
Observations	1,440	1,438	1,438	660	778	247	187	841					
<i>R</i> ²	.011	.018	.019	.024	.015	.041	.061	.021					

Notes: Beta coefficients and robust standard errors clustered on the interview date presented.

* $p < .01$;

**
* $p < .05$;

* $p < .1$. Quadratic specification adds a squared term for the running variable (interview date). Interactions specification adds an interaction term between the interview date and the treatment variable. Additional controls not shown: age (ns), other race (ns), Indian race (ns), Asian race (ns), constant.