Culture as a Mediator of Gene-Environment Interaction:

Cultural Consonance, Childhood Adversity, a 2A Serotonin Receptor Polymorphism, and

Depression in Urban Brazil

William W. Dressler
Department of Anthropology
The University of Alabama

Mauro C. Balieiro
Department of Psychology
Paulista University

Luiza Ferreira de Araújo
Department of Genetics
Ribeirao Preto Medical School
University of Sao Paulo-Ribeirao Preto, and
Center for Medical Genomics at HCFMRP/USP

Wilson A. Silva, Jr.
Department of Genetics
Ribeirao Preto Medical School
University of Sao Paulo-Ribeirao Preto, and
Center for Medical Genomics at HCFMRP/USP

José Ernesto dos Santos
Department of Internal Medicine
University of São Paulo-Ribeirão Preto

Corresponding author: William W. Dressler
Department of Anthropology
The University of Alabama
PO Box 870210
Tuscaloosa, AL 35487-0210
wdressle@ua.edu
205-348-5947 (v)
205-348-7937 (f)

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Abstract

Research on gene-environment interaction was facilitated by breakthroughs in molecular biology in the late 20th century, especially in the study of mental health. There is a reliable interaction between candidate genes for depression and childhood adversity in relation to mental health outcomes. The aim of this paper is to explore the role of culture in this process in an urban community in Brazil. The specific cultural factor examined is cultural consonance, or the degree to which individuals are able to successfully incorporate salient cultural models into their own beliefs and behaviors. It was hypothesized that cultural consonance in family life would mediate the interaction of genotype and childhood adversity. In a study of 402 adult Brazilians from diverse socioeconomic backgrounds, conducted from 2011 to 2014, the interaction of reported childhood adversity and a polymorphism in the 2A serotonin receptor was associated with higher depressive symptoms. Further analysis showed that the gene-environment interaction was mediated by cultural consonance in family life, and that these effects were more pronounced in lower social class neighborhoods. The findings reinforce the role of the serotonergic system in the regulation of stress response and learning and memory, and how these processes in turn interact with environmental events and circumstances. Furthermore, these results suggest that gene-environment interaction models should incorporate a wider range of environmental experience and more complex pathways to better understand how genes and the environment combine to influence mental health outcomes.

It is widely accepted that mood and mental disorder are a function both of genetic predisposition and experience in the social environment. The belief has been that genes and the environment interact to influence psychological distress, but the empirical examination of this interaction has been problematic, limited to the constrained research designs offered by twin studies and quantitative genetics (Dick, Agrawal, Keller et al. 2015).

Modern techniques of molecular biology changed everything. Individual participants in research can now be genotyped and the synergistic effects of genetic inheritance and social experience specified. Research by Caspi and associates (2003) began a flurry of papers examining these effects. In less than a decade, the number of papers examining gene-environment interactions in relation to depression made possible a meta-analysis of those studies (Risch, Herrell, Lehner et al. 2009). This meta-analysis in turn stimulated serious controversy regarding the actual existence of GxE (or “gene times environment”) effects (Duncan, Polastri & Smoller 2014).

The aim of this paper is to enter into this controversy from a specific perspective comprising two main issues. First, the focus on the environmental side of the equation has been limited. The range of human experience in the social environment has been examined using only a few variables. Second, the emphasis has been on direct paths from GxE to mood states, without a consideration of potential intervening variables. We will present a model of gene-environment interaction, drawing on data collected in urban Brazil, suggesting that a more nuanced view of human social experience rooted in the context of culture must be taken into account. Specifically, we will present evidence that cultural consonance mediates the interaction between childhood adversity and a serotonin receptor polymorphism, and that this mediation is itself moderated by social class.

Gene-Environment Interactions and Depression

The basic GxE hypothesis is that individuals exposed to the same environmental events experience them differently depending on those individuals' specific genotypes, in turn altering the expression of depressive symptoms. Most research has focused on childhood adversity and/or stressful life events. Studies have found an interaction of these factors with genes for: (a) the serotonin transporter (Caspi et al. 2003); (b) the 2A receptor for serotonin (Mellman, Alim, Brown et al. 2009); (c) the D2 dopamine receptor (Keltikangas-Jarvinen & Salo 2009); and, (d) brain-derived neurotrophic factor (Kaufman, Yuang, Palumberi et al. 2006), among others.

The short history of studies of GxE has already generated controversy. With respect to the serotonin transporter gene specifically, a meta-analysis by Risch and associates (2009) concluded that there was no evidence of a consistent gene-environment interaction when studies were combined, suggesting that the original results of Caspi and associates, and other studies that followed, represented false positive findings. Others have countered that this meta-analysis is flawed because of the variety of (noncomparable) ways in which the environmental side of the equation—childhood adversity and stressful life events—has been operationalized (Monroe & Reid 2008). Caspi and associates, in a qualitative review of studies, concluded that there was indeed a replicable GxE effect, and that it was most consistent when childhood adversity (e.g., the death of a parent, inconsistent or severe socialization) was assessed in combination with genotype (Caspi, Hariri, Holmes et al. 2010).

From a logical standpoint, some researchers have argued that the “candidate gene” approach is flawed from the outset. This is based on the belief that any complex phenotype such as mood or depression is unlikely to be influenced by any one or even several genes, but rather by the additive and interactive effects of many genes operating simultaneously in the presence of

environmental events and circumstances. This argument implies that only genome-wide scans have any chance of detecting reliable effects. This necessitates large samples, expensive genetic analyses, and, if gene-environment interactions are to be taken seriously, complex research designs (Duncan, Polastri & Smoller 2014).

We approach this research from a slightly different perspective, consistent with the recent review of research by Dick and colleagues (2015). These authors argue that candidate gene studies are still useful when there is a plausible biological pathway for the gene in question and when the analysis is guided by a clear theory. With respect to the development of theory of gene-environment interaction, there are two notable issues to be addressed. First, the conceptualization of “the environment” in GxE research has been very constrained (Manuck & McCaffery 2014). The majority of studies have relied only on stressful life events or childhood adversity as measures of environmental stimuli. Despite a few notable exceptions (especially Kaufman et al. 2006), there has been little consideration given to other kinds of experience in the social environment as relevant to the study of gene-environment interactions. That this is an impoverished view of human social life and psychological adjustment almost goes without saying.

Second, analyses of GxE in relation to psychological distress have almost always specified the gene-environment interaction as involving a direct path to the outcome. There has been little consideration given to the possibility (or even likelihood) that other factors intervene between the gene-environment interaction and the psychological outcome. This is especially important given the fact that, as Caspi et al. (2010) show, the interaction of childhood adversity and genotype is particularly important as a predictor of depression in adulthood. With the variety of concurrent predictors of depressive symptoms in adulthood, it seems likely that the

GxE involving childhood adversity is more distal in the causal chain. A mediation hypothesis is thus attractive.

In this paper, we present a model in which the association with depression of the interaction between childhood adversity and a polymorphism in the serotonin 2A receptor is mediated by cultural consonance in family life. Furthermore, the observed associations are most pronounced among lower class respondents in Brazil.

Cultural Consonance and Depressive Symptoms in Urban Brazil

Over the past three decades our research group has investigated culture as a factor in human health. This research has necessitated the development of both theory and method to identify and measure how culture is manifest at the level of the individual. The concept of cultural consonance has guided this work. Cultural consonance is the degree to which individuals approximate, in their own beliefs and behaviors, the prototypes for belief and behavior encoded in cultural models (Dressler 2007).

The concept of cultural consonance is derived from a cognitive theory of culture. Culture is defined as the knowledge one must possess to function adequately in a given social system (Goodenough 1956). This knowledge is stored cognitively in the form of schema and models. These are stripped-down, skeletal representations of objects, experience, and cultural domains. The more comprehensive of these cognitive structures is the cultural model, consisting of the elements that make up a cultural domain; the semantic and functional relationships among those elements; and, one or more prototypes that represent typical instantiations of the model. What makes a model cultural is that it is shared and learned in social interaction. Daily life is guided by multiple models that interdigitate in complex ways. Cultural models guide the behavior of individuals as well as enabling those individuals to more or less correctly interpret the behavior

of others. Furthermore, while cultural models are stored in the minds of individuals, given the shared nature of those models it is useful to think of them as existing across minds as well as within them, thus accounting for the aggregate quality of culture (D'Andrade 1995).

The study of cultural models has been enhanced by the development of cultural consensus analysis. This is a statistically and theoretically satisfying way of verifying the sharing of a cultural model, something that generally has been merely assumed in anthropology. In addition to verifying the degree to which a cultural model is shared, cultural consensus analysis can be used to specify the culturally constructed knowledge within a cultural domain (Romney, Weller & Batchelder 1986).

The measurement of cultural consonance, however, requires a further step. For a variety of reasons, ranging from conscious choice to motivation to, especially, socioeconomic resources, not everyone can act on shared knowledge to implement in their own lives the goals encoded in cultural models. This is the essence of cultural consonance. Individuals are variably able to act on shared knowledge. There will thus be a distribution of cultural consonance in society, with some individuals achieving a very close fit to the consensus model, while others' lives only marginally approximate those models.

In research in Brazil, we have concentrated our attention on a set of cultural models linked by their centrality as life span developmental goals. The cultural domains were selected for analysis on the basis of both theory and the prominence of those domains in mundane conversation in Brazil. These include: lifestyle (material goods and leisure activities that contribute to "having a life"); social support (the presence of a network of individuals on whom one can rely for help in times of felt need); family life (the characteristics that contribute to "having a family"); national identity (how one matches the characteristics defining a social being

in Brazil); and, occupational and educational satisfaction. Cultural consensus models were identified in each of these domains, and that consensus extended across social class (Dressler, Borges, Balieiro & Santos 2005; Dressler, Balieiro & Santos 2015). Cultural consonance in each of these domains is associated with health outcomes, and cultural consonance mediates the effect of social class on psychological distress (Dressler, Balieiro, Ribeiro & Santos 2015).

With respect to psychological distress, cultural consonance in family life has proven to be of particular importance (Dressler 2005). Cultural consonance in family life was found to be the strongest predictor of depressive symptoms in a prospective study (Dressler, Balieiro, Ribeiro & Santos 2007), and as da Matta (1985) and others have argued, the cultural domain of the family is highly salient in Brazilian society (Almeida 2007; Wagley 1971). This means that the family is a special focus of emotional energy in Brazilian daily life. Being unable to achieve shared goals in life that are defined by the cultural model of the family is a profoundly stressful experience. On one hand, the individual sees him- or herself as not living up to a widely acknowledged understanding of what a prototypical family is like. This can lead to a sense of loss and social failure that underlie depressed affect. On the other hand, cultural consonance can mediate mundane social interaction. Cultural consonance helps to define our presentation of self in social interaction, and hence how others view us. Where cultural consonance is low, especially in highly salient domains, others may not accord us the same degree of respect as those who are seen to be more culturally successful. Such micro-stressors in social interaction can in turn induce feelings of helplessness and hopelessness and, ultimately, depression.

Gene-Environment Interaction and Cultural Consonance

As noted above, much of the research on gene-environment interactions and depression has focused on genes in the serotonergic system. Serotonin is a neurotransmitter linked to the

regulation of emotion, learning, memory, decision-making, and the stress response (Buhot 1997; Yildirim & Derksen 2013). Serotonergic neurons originate in a relatively small area at the base of the brain, yet extend throughout the entire brain and represent the largest system of neurons. When a nerve impulse is transmitted via serotonin, it binds to one of 15 receptors on the receiving cell. One of these, the 2A receptor, is highly represented in the prefrontal cortex of the brain, and the functioning of that receptor is linked to executive functions involving learning, memory, and the regulation of emotion (Yildirim & Derksen 2013). Furthermore, there is a well-described single nucleotide polymorphism (or SNP) in the serotonin 2A receptor that has been shown to be biologically active in two ways. In research at the cellular level, cells with two A alleles for this SNP process genetic information at a higher rate than cells with a G and an A or two G alleles (Parsons, D'Souza, Arranz et al. 2004). In studies of the treatment of depression, persons with the AA genotype who have been diagnosed with depression respond better to the atypical antidepressants in treatment (McMahon, Buervenich, Charney et al. 2006).

In a pilot study involving a nonrandom subsample of 144 individuals drawn from a larger community sample, we examined the interaction between this SNP in the 2A receptor (-1468GA; rs6311) and cultural consonance in family life (Dressler, Balieiro, Ribeiro & Santos 2009). Persons with two A alleles for this gene had higher depressive symptoms in association with low cultural consonance than persons with the GA or GG genotypes, and they had lower depressive symptoms in association with high cultural consonance than persons with other genotypes. The alternative variants of this polymorphism appear to define what Ellis and Boyce (2008) refer to as a “biological sensitivity to context.” That is, under one set of biological conditions—the presence of the AA genotype—individuals are more reactive to experience in the social environment, while under conditions defined by the other genetic variants, they are less reactive

(see Belsky, Jonassaint, Pluess, et al. 2009 for a similar argument). Note too that this biological sensitivity works in both directions, in the sense that positive experience in the social environment leads to stronger positive outcomes, while negative experience leads to stronger negative outcomes.

The new research presented in this paper was conducted specifically to replicate the pilot study and to test the potential mediating role of cultural consonance in relation to other widely studied GxE effects, especially the interaction of childhood adversity and genotype. As we have reported elsewhere, we failed to replicate the cultural consonance-genotype interaction with these new data (Dressler, Balieiro, Araújo, Wilson & Santos 2016). Thus, our aim in this paper is to examine the role of cultural consonance in mediating the impact of the interaction between childhood adversity and the serotonin 2A receptor polymorphism on depressive symptoms.

This hypothesis is guided both by our theory of cultural consonance and Beck's (2008) cognitive theory of depression. In Beck's theory, problematic events or circumstances in early life lead an individual to develop a set of negative beliefs, or what Beck refers to as "a dysfunctional personal schema." That is, the individual generalizes from problematic experience that he or she is incapable of dealing adequately with the world and that the inevitable outcome of effort is failure. Furthermore, the prominence and negative emotional valence of these negative events are exacerbated among children who are genetically sensitive to social context (Beck 2008: 972-974). Thus, this dysfunctional personal schema becomes a more or less fixed way of interpreting events and circumstances. Ultimately, repeated negative self-evaluations lead to depression.

When problematic events in childhood involve the family, we hypothesize that this dysfunctional personal schema is specifically a dysfunctional family schema. Such a

dysfunctional schema could lead to conflict in interpersonal relationships in later life that impede the development of a family that matches the cultural model of the Brazilian family.

Additionally, this dysfunctional schema could interfere with learning the cultural model of the family, in turn leading to lower cultural consonance in family life. By either pathway, the gene-environment interaction may lead first to lower cultural consonance, and then ultimately to higher depressive symptoms.

Ethnographic Background

Research was carried out in Ribeirão Preto, Brazil, an urban center (pop. = 600,000) in the state of São Paulo manifesting the same extremes of wealth and poverty as all of Brazil. Research in Brazil must account for income inequality. In our survey research, we have worked in four neighborhoods differing in socioeconomic status. The poorest neighborhood studied began as a *favela* or squatter settlement. Typically, persons living in a *favela* work as unskilled laborers in agriculture or industry, and as domestic servants. During a period of urban renewal, this *favela* was razed by the municipality and all the residents moved to a public housing project. The neighborhood has evolved considerably, although it still carries an unsavory reputation for crime and drug-trafficking, associated in part with its past as a *favela*.

The second neighborhood sampled was a *conjunto habitacional*. A *conjunto* is a housing development constructed in partnership between a municipality and a developer. The houses begin as small (4 rooms) cinder block dwellings on the very edge of the city. The municipality supplies neighborhood services and helps to underwrite low-cost loans for the purchase of the houses. Owners qualify for such loans on the basis of stable employment. The *conjunto* studied here was begun shortly before 1991 and developed very quickly. Houses were modified rapidly,

with added rooms, floors, and garden walls. The former *favela* and the *conjunto habitacional* together can be considered “lower income neighborhoods.”

The third neighborhood sampled was a traditional middle-class neighborhood, begun at the turn of the 19th century by Italian immigrants to Ribeirão Preto. At its founding this neighborhood was on the edge of the city proper, but has since been entirely engulfed. Houses are much larger than those in the *conjunto*, and like some European cities, they present an unbroken wall to the street. Some streets are still cobbled, and the neighborhood is dominated by a large *praça* or square with a Catholic church. Although occupational pursuits are quite varied, many residents are professionals such as teachers and nurses, and many others are small-scale businesspersons or work as managers in larger enterprises.

The final neighborhood sampled was a gated, upper-middle class subdivision. The houses verge on being enormous, with extensive and well-tended gardens. The residents of this neighborhood are upper-level professionals such as physicians, attorneys, and university professors. This and the traditional middle-class neighborhood can be considered “higher income neighborhoods.”

It is important to consider the potential impact of social class on the entire process examined here. Residence is strongly associated with social class in Brazil and, despite gains made in recent years, income inequality is considerable. The lower classes have little access to the resources that middle and upper class Brazilians have, and this may be important with respect to individuals’ resilience in the face of childhood adversity.

Methods

This research was carried out from 2011-2014, building on two previous studies. The measurement of cultural consonance used here was derived in 2001 and re-evaluated and verified

in the current study (Dressler et al. 2005, 2015). Measuring cultural consonance requires a specialized approach, referred to as an “emic” approach in anthropology. The emphasis is on discovering and employing the categories that people in the community under investigation themselves use to think and talk about a given domain. Therefore, rather than the investigator deciding at the outset what the important elements of family life are, in an emic approach we employ specialized interviewing techniques and analyses to discover the terms that Brazilians use to talk about the family. This cultural domain analysis culminates in a cultural consensus analysis to identify what a sample of Brazilians agree are the most important elements of family life. We found that respondents grouped terms describing the family in categories referring to: structure and organization of the family; emotional climate within the family; and behaviors that threaten family cohesion.

These results are then used to derive measures of cultural consonance in each domain. The emphasis thus shifts from the group to the individual. In measuring cultural consonance in family life we developed Likert-response items (weighted by their importance in the cultural consensus analysis) for each of the family terms elicited in the cultural domain analysis. The respondent evaluated his or her own family on these terms. To the extent that a respondent agrees that his or her family can be characterized in this way, that individual’s family matches the cultural model of family life. A measure of cultural consonance has high “emic validity” in that it orders individuals along a continuum defined in the terms that they themselves use to talk and think about that domain (Dressler & Oths 2014).

Once the structure of a cultural domain has been investigated, cultural consensus has been verified, and measures of cultural consonance have been developed, conventional social survey research can be carried out to test hypotheses regarding the associations of cultural

consonance with outcome variables, relative to other factors. The cultural domain analyses and the derivation of the measures of cultural consonance have been described in detail elsewhere (Dressler et al. 2005, 2015). Here we focus on the survey component of the research. This research was approved by the Institutional Review Board for the Protection of Human subjects of the University of Alabama and by the Ethics Committee of the Faculty of Medicine of the University of São Paulo.

Sampling

Survey data were collected from representative samples from four neighborhoods (described briefly above) differing in socioeconomic status and used as sampling strata. Maps identifying households were produced for each neighborhood. For each block in each neighborhood, households selected randomly were visited by interviewers (graduate-level Brazilian psychology students, trained by the authors). A single adult over the age of 18 was randomly selected from each household. Households were dropped from the sample if three visits produced no contact. The final sample size with complete data was $n = 402$, representing a response rate of 39%. (There is no overlap between this sample and the sample on which the pilot study was based.)

Measurements

Survey data were collected in face-to-face interviews conducted in the home. The Center for Epidemiological Studies Depression Scale (CES-D) was the dependent variable. This is a 20-item scale of common symptoms of depression. Respondents report the frequency of the experience of each symptom during the previous two weeks on a 4-point scale. This scale was translated and validated independently by Brazilian researchers (da Silveira, Jorge, Gorenstein, Andrade & Zuairi 2000). In the current sample the reliability is satisfactory ($\alpha = .91$).

Covariates include age (in years); gender (women = 0, men = 1); and socioeconomic status (a factor score combining family income, respondent's completed educational level, and respondent's occupational prestige score).

Cultural consonance in family life was measured with an 18-item, Likert-response scale created from the results of the consensus analysis. Each item assessed the respondent's perception of his/her own family in the terms derived from the cultural domain analysis. Each item was also weighted by its salience in the consensus analysis. The scale has high internal consistency reliability ($\alpha = .91$), and is described in more detail elsewhere (Dressler et al. 2005). Sample items include the following: (a) "Sometimes I wish my family were more organized" (reverse coded to assess family structure and organization); (b) "In my family we feel close to one another" (to assess emotional climate); and, (c) "When I do something, I don't think about my family" (to assess threats to the family). (The entire scale is presented in Supplemental Table 1.)

INSERT LINK TO ONLINE FILE 1 HERE.

Childhood adversity was assessed with a checklist of problematic events that may have occurred during the respondent's upbringing. Only the events occurring within the family were counted to arrive at a score for childhood adversity. These included: severe illness of the respondent; severe illness or death of parent (2 items); severe illness or death of sibling (2 items); drug use by family members; abuse by family members; and, parental neglect.

Samples of cheek cells were collected using brush swabs. Respondents rinsed their mouths with water before using the swab to collect cells from both cheeks and the gum line. Individuals' genomic DNA was isolated using the BuccalAmp DNA Extraction Kit (Epicentre). A single nucleotide polymorphism for the serotonin 2A receptor (5' UTR; rs6311) was

genotyped using the Taqman Pre-Designed SNP Genotyping Assay (Life Technologies). PCR amplification and allelic discrimination were performed with the 7500 Fast Real-Time PCR system (Life Technologies), according to product specifications. Validation of each Taqman Assay was performed using controls of known genotypes. To assess the genotyping error rate, 5% of the sample was genotyped in duplicate. There was 100% of concordance. (A second polymorphism, for a gene coding for brain-derived neurotrophic factor, was included, based on the work of Kaufman et al. (2006). This polymorphism had no significant interaction with childhood adversity, although there was a significant interaction with concurrent stressful life events in relation to depressive symptoms. Those results will be discussed in a subsequent report.)

Data were analyzed using ordinary least squares multiple regression analysis, with gene-environment interactions tested using standard techniques of interaction cross-products involving one continuous and one dichotomous variable (Cohen, Cohen, West & Aiken 2003).

Results

Table 1 presents data for the sample as a whole, and broken down by the two lower income and the two higher income neighborhoods. As noted, all measured variables differ

INSERT TABLE 1 ABOUT HERE

significantly between lower and higher income neighborhoods, with the exception of the distribution of genotype and gender. (Bivariate correlation matrices are presented in Supplemental Table 2.)

INSERT LINK TO ONLINE FILE 2 HERE

Table 2 presents the analysis of the gene-environment interaction between the 2A receptor polymorphism and childhood adversity in relation to depressive symptoms. In this

analysis the AA genotype is coded 1 and the GG/GA genotypes are coded 0 (these were combined to preserve degrees of freedom and because the primary effect of genotype is anticipated to be for the persons homozygous for the A allele). The regression coefficient for the “main effect” of childhood adversity is, in the presence of a significant childhood adversity-genotype interaction, actually the effect of childhood adversity within the group of respondents with the AA genotype. The regression coefficient for the interaction effect reflects the amount by which that effect is altered if the respondent has a GG or GA genotype.

INSERT TABLE 2 HERE

In Table 2 results are presented for the sample as a whole, and broken down by neighborhood. There is a significant gene-environment interaction, and that interaction is concentrated among respondents in lower income neighborhoods (although the three-way interaction among genotype, childhood adversity, and neighborhood is not statistically significant). The shape of the interaction is shown in Fig. 1, for the two lower income neighborhoods (standardized regression coefficients shown in the figure have been calculated from those reported in Table 2 to express the within-genotype effect). Among persons with the AA genotype for the 2A receptor, as childhood adversity increases, depressive symptoms increase as well. Among persons with either the GA or GG genotypes, there is no association between childhood adversity and depressive symptoms. Another way of expressing this effect is to contrast the percent difference in symptom levels for persons within the lower social class neighborhoods with high childhood adversity (1 standard deviation above the mean) versus persons with low childhood adversity (1 standard deviation below the mean), and different genotypes. Persons with the AA genotype and high childhood adversity report about 45% higher depressive symptoms levels than persons with low childhood adversity, while persons with the

GA or GG genotypes and high childhood adversity report about 5% higher depressive symptoms than persons with low childhood adversity.

INSERT FIG. 1 HERE

Cultural consonance in family life was then entered into the analysis, as shown in Table 3. When cultural consonance is controlled for, the interaction of childhood adversity and genotype becomes non-significant.

INSERT TABLE 3 HERE

If cultural consonance in family life can be considered to have a mediating effect between the gene-environment interaction and depressive symptoms, the gene-environment interaction should have an association with cultural consonance in family life. This analysis is shown in Table 4, and the shape of the interaction is shown in Fig. 2 for lower income respondents. Among persons with the AA genotype, as childhood adversity increases, cultural consonance in family life decreases. Among persons with the GA or GG genotypes, there is no association. (Again, standardized regression coefficients shown in the figure have been calculated from those reported in Table 4.)

INSERT TABLE 4 HERE

The statistical significance of the mediating effect of cultural consonance in family life for the genotype-childhood adversity interaction was evaluated using the Sobel test (Baron and Kenny 1986). These results indicate that the effect of the gene-environment interaction operating through cultural consonance in family life is statistically significant for the sample as a whole ($p = .003$) and within the lower income neighborhoods ($p = .001$).

INSERT FIG. 2 HERE

Discussion

These results are consistent with a model in which the interaction between childhood adversity and the –1468 G/A polymorphism (rs6311) in the 2A serotonin receptor in relation to depressive symptoms in adulthood is mediated by cultural consonance in family life. The findings are summarized in Fig. 3. The evidence suggests that the 2A receptor polymorphism alters the individual's sensitivity to his or her social context (Ellis & Boyce 2008). Where childhood adversity is low, especially in the lower income neighborhoods, cultural consonance in family life is higher among persons with the AA genotype versus other gene variants; where childhood adversity is high, cultural consonance in family life is lower among persons with the AA genotype versus other gene variants (see also Belsky et al. 2009). Then, low cultural consonance in family life is associated with higher depressive symptoms.

INSERT FIG. 3 HERE

Furthermore, all of these associations are more pronounced among lower social class respondents. The ethnographic significance of this moderation by social class in the Brazilian context outweighs the fact that the three-way interaction of childhood adversity, genotype, and neighborhood is not statistically significant. (The lack of statistical significance is likely a result of the relatively small numbers of subjects who are upper income, have the AA genotype, and who have experienced substantial child adversity.) Brazil as a society is one of the most unequal in the world (Dressler et al. 2015). Life in lower class neighborhoods can be unpredictable and dangerous as families face daily struggles to make ends meet on modest incomes in the context of high crime rates, drug trafficking, harassment by police, and other social ills. The experience of childhood adversity in the context of low social class, and in the presence of a genetic polymorphism that can exacerbate reactivity to environmental events, would be an especially

problematic combination with respect both to psychosocial adjustment and preparation for adult roles.

It is paradoxical, and worth noting, that the effect of cultural consonance on depression occurs as a result of the fact that the cultural model of the family is shared across social class lines, but that social class in turn constrains individuals' ability to achieve that cultural consonance. Low cultural consonance is thus nearly inevitable for some (Dressler et al. 2015).

A consideration in interpreting these results must be the accuracy of the respondents' recall of childhood adversity that, in general, occurred to them forty years earlier. There is no way to determine if these self-reports are accurate. However, the accuracy of reporting childhood adversity is not really the issue. The respondent who reports higher childhood adversity believes him- or herself to have experienced this. Put perhaps more accurately, the respondent has a personal schema regarding childhood in which his or her representation of life in the family of orientation included this adversity. Regardless of whether it occurred or not, having this schema for childhood increases the likelihood that one will also report depressive symptoms in the presence of a particular genetic variant of the 2A receptor. So the "reality" of childhood adversity is a non-issue, although we are inclined to believe that, given the nature of the events, it is likely that in most instances they actually occurred.

Tracing the entire biocultural process by which variables from the molecular to the cultural combine and interact to produce particular psychological outcomes is likely to go beyond existing evidence; nevertheless, at least a speculative sketch of that process would be useful. It of course starts with the polymorphism in the 2A receptor, present at birth. Some children are born with a higher biological sensitivity to their social context, which is a function both of the greater translational efficiency of the 2A receptor in the AA genotype, and of greater

density of the receptors in the prefrontal cortex in the AA genotype (Yildirim & Derksen 2013: 1274). Higher serotonergic activity in the prefrontal cortex is in turn associated with greater reactivity in the amygdala in response to threatening emotional stimuli (Fisher, Price, Meltzer et al. 2011).

In this study, those threatening emotional stimuli involve the occurrence of traumatic family events in childhood. And, given the cultural salience of the family in Brazil, these events are likely to have a strong emotional impact, especially in the context of the lower class, given fewer material resources to absorb the effect of an event (e.g., the death of a parent). Following Beck (2008), the individual experiencing childhood adversity develops a dysfunctional personal schema that colors his or her understanding of everyday life. The child comes to assume that the adversity and emotional turmoil he or she is experiencing is something that will continue on, in other contexts.

The child then matures as an adult to establish his or her own family. While the individual is likely assuming some degree of cultural competence in the Brazilian model of the family, his or her interpersonal interactions are hampered by both an emotional reactivity to events and circumstances, and by the dysfunctional personal schema coloring his or her worldview. These combine to constrain that individual's ability to achieve consonance with the cultural model of the family. The disparity between what is culturally valued and what is personally achieved is, consciously or not, apparent to the individual, in turn contributing to a sense of helplessness and hopelessness. Ultimately, this lack of cultural consonance describes, in part, the individual's presentation of self in everyday life, where he or she is seen by others not to have achieved success in this salient cultural domain. When status confirmation is repeatedly

withheld in mundane social interaction, the distress experienced by the individual is compounded, further contributing to depressed affect.

It is important to emphasize immediately, of course, that precisely the opposite occurs for the individual with the AA genotype who is not exposed to adversity in childhood. This individual, rather, experiences a cultural success in family socialization, enhanced by a positive emotional reactivity, that ultimately results in a higher adult cultural consonance in family life and lower risk of depression. And, for persons with the GA or GG genotypes, childhood adversity is not related to their ultimate learning and implementing of the cultural model in their own lives, and cultural consonance in family life remains a potent correlate of depressive symptoms.

This of course is a provisional account of this biocultural process, but one that is nevertheless consistent with current research. Perhaps the point to emphasize is that this explanatory sketch avoids a crude reductionism and instead combines processes from the molecular to the psychological to the cultural. It is the interaction of these processes across levels of system integration and across the life span that result in individual differences in psychological outcomes.

Regardless of specifically how the interaction of genes, psychological factors, and culture underlie the results observed here, these findings offer several directions for future research on gene-environment interactions. First, more hypotheses involving the mediation of GxE effects should be developed.

Second, these results suggest that GxE effects are socially and culturally contextualized at several levels. One has already been noted: the gene-environment interaction effect as mediated by cultural consonance in family life is exacerbated in lower class neighborhoods. A

second level of contextualization involves cultural context in a broader sense. Why is this childhood adversity-genotype interaction mediated by cultural consonance in family life? It would be straightforward to think that since childhood adversity is assessed in the context of the family it would in turn create family difficulties for adults. At the same time, this mediating process may be particularly strong because the research was conducted in Brazil. As numerous commentators have observed, the family assumes a significance in Brazil not found everywhere (da Matta 1985). The family is the center of life for Brazilians. It might be, therefore, that the mediation of this GxE effect by cultural consonance in family life is because of the cultural salience of the family in Brazil, and that in other settings other mediators might be important. The mediating effect of cultural consonance in other domains (lifestyle, social support) was also tested, and these other measures of cultural consonance did not mediate the GxE effect. This bolsters the potential importance of the overall salience of the cultural domain in a particular setting as being of relevance.

Finally, a third level of contextualization can be seen in the mediation of the GxE effect specifically by a measure of cultural consonance. As emphasized earlier, this measure was designed to maximize emic validity. It is constructed specifically in the terms that Brazilians use to talk and think about the family. As such, its validity is relative to that setting.

The social and cultural contextualization of these results is at odds with the current tenor of the literature on gene-environment interactions (Duncan et al. 2014). Indeed, in this literature it is assumed not only that an individual's genotype can be assessed independently of his or her social and cultural setting, but that meaningful experience in the social environment also can be assessed independently of context. These assumptions justify meta-analyses of gene-environment effects on depressive symptoms. To the extent to which these assumptions are

rendered problematic, as the results here suggest, meta-analyses are equally suspect. We of course are not saying that meta-analyses of the type published by Risch and associates (2009) should not be conducted. These are helpful in thinking about the literature. What we are saying, however, is that the ethnographic context of the research must be taken into account as well in evaluating research results.

The model proposed here also bears on the controversy surrounding the candidate gene approach versus the genome-wide scan approach (Manuck & McCaffery 2014). Critics of the candidate gene approach engage in speculation about the number of potential genes that can influence complex phenotypes, then extrapolate to the number of main and interaction effects possible, concluding that because these numerous effects are unaccounted for in the candidate gene approach, any single finding is likely to be a false positive result (Duncan et al. 2014). However, if gene-environment interactions are conditioned by the cultural context in which they occur, as we suggest here, without the specification of that context along with culturally constructed mediating variables, genome-wide scans are likely to miss relevant effects. Again, we are not attempting to argue against genome-wide scans; rather, we suggest that there is no royal road to understanding gene-environment interactions.

There are limitations to this research that should be noted. While we think the candidate gene approach is useful, the number of polymorphisms for which significant GxE effects have been observed indicate that multiple genes are implicated in these processes and that future research should follow the lead of Beaver & Belsky (2012) and especially Disner, McGeary, Wells, Ellis & Beevers (2014) by developing multi-gene indicators. Disner and associates' (2014) work is particularly intriguing as they developed a multi-gene indicator employing only polymorphisms in the serotonin system. Given the potential importance of the serotonin system

in learning, memory, and the regulation of emotion, this is an important way to proceed.

Additional limitations in the current paper include typical problems of sampling, potential unreliability in the measurement of variables, and possible model misspecification.

Ultimately, the results presented here are useful in that they suggest new avenues for the study of gene-environment interactions. Complex phenomena like mood disturbances are clearly multifactorial. Furthermore, the influence of some of those factors can be moderated within the context of culture. Gene-environment interactions thus need to be integrated into more comprehensive, biocultural models.

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Figure titles:

Fig. 1: Interaction of genotype and childhood adversity in relation to depressive symptoms:
lower income neighborhoods

Fig. 2: Interaction of genotype and childhood adversity in relation to cultural consonance in
family life: Lower income neighborhoods

Fig. 3: A model of the mediation of gene-environment interaction by cultural consonance

Table 1: Descriptive statistics

Variables:	Total sample (n = 402)	Lower income neighborhoods (n = 198)	Higher income neighborhoods (n = 204)
Depressive symptoms	18.7 ($\pm$ 13.4)	22.0 ($\pm$ 14.0)	15.5 ($\pm$ 12.1)
Age	48.7 ($\pm$ 14.4)	46.5 ($\pm$ 13.6)	50.8 ($\pm$ 14.9)
Gender (% men)	33.0	30.0	35.0
SES*	0.00 ($\pm$ 1.0)	-0.46 ($\pm$ 0.72)	0.48 ($\pm$ 1.0)
Childhood adversity	2.40 ($\pm$ 1.6)	2.80 ($\pm$ 1.6)	2.00 ($\pm$ 1.4)
Cultural consonance in family life	101.20 ($\pm$ 29.9)	94.60 ($\pm$ 30.1)	107.60 ($\pm$ 28.3)
Genotype (%)			
GG	14.9	14.6	15.2
GA	57.0	57.6	56.4
AA	28.1	27.8	28.4

*SES = socioeconomic status

Note: All differences between neighborhoods are significant at $p < .01$ except for gender and genotype.

Table 2: Regression of depressive symptoms on childhood adversity and genotype for the total sample and within lower and higher income neighborhoods (standardized regression coefficients)

Variables	Total sample	Lower income neighborhoods	Higher income neighborhoods
Age	-.12**	-.13	-.09
Gender	-.14**	-.13	-.16*
SES	-.20**	-.16*	-.11
Genotype (GG/GA vs. AA)	-.11*	-.06	-.16*
Childhood adversity	.29**	.35**	.23
Childhood adversity x genotype	-.17*	-.26*	-.09
R	.37*	.33**	.30**
R ²	.14	.12	.09

*p < .05

**p < .01

Table 3: Regression of depressive symptoms on childhood adversity, genotype, and cultural consonance in family life for the total sample and within lower and higher income neighborhoods (standardized regression coefficients)

Variables	Total sample	Lower income neighborhoods	Higher income neighborhoods
Age	-.07	-.05	-.05
Gender	-.14**	-.14*	.14*
SES	-.11*	-.08	-.05
Genotype (GG/GA vs. AA)	-.08*	-.04	-.14
Childhood adversity	.16*	.15	.17
Childhood adversity x genotype	-.10	-.13	-.08
Cultural consonance in family life	-.41**	-.48**	-.31**
R	.53**	.57**	.42**
R ²	.29	.32	.18

*p < .05

**p < .01

Table 4: Regression of cultural consonance in family life on childhood adversity and genotype for the total sample and within lower and higher income neighborhoods (standardized regression coefficients)

Variables	Total sample	Lower income neighborhoods	Higher income neighborhoods
Age	.13**	.15*	.10
Gender	.02	-.03	.06
SES	.21**	.17*	.17*
Genotype (GG/GA vs. AA)	.06	.03	.06
Childhood adversity	-.31**	-.42**	-.18
Childhood adversity x genotype	.16 ⁺	.27*	.03
R	.35**	.33**	.26*
R ²	.12	.10	.07

⁺p = .06 *p < .05 **p < .01