

A Longitudinal Study of Genes, Culture, and Depression in Urban Brazil

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ABSTRACT Stressful life events and cultural consonance in family life (the correspondence between individuals' perceptions of their families and cultural models of the family) are independent predictors of depressive symptoms in a Brazilian community. The moderating effect of the gene for a receptor for serotonin was examined. For individuals with the A/A variant of the -1438G/A polymorphism of the 2A serotonin receptor, stressful life events and cultural consonance in family life have stronger effects on depressive symptoms over a 2-year period than for individuals with other variants of the gene. The implications of these results for biocultural theory are discussed.

The investigation of the interaction of genotype and culture has long been a goal of biocultural studies in anthropology. With the mapping of the human genome, opportunities exist to directly investigate the interaction of genes and culture as predictors of individual adaptation. What perhaps impedes this research most now is the difficulty of conceptualizing culture in a way that is both theoretically satisfying and methodologically rigorous. Minimally, a theory of culture must link shared meaning at the level of social aggregates to the beliefs and behaviors of individuals. A recent theory of "cultural consonance" offers the promise of providing such a link. Cultural consonance, as a concept and a measure, links the cultural to the individual, and potentially to the biological (Dressler 2005).

In this paper we will examine the interaction between cultural consonance, stressful life events, and a polymorphism in the gene for a receptor in the serotonin system as predictive of depressive symptoms in a community sample drawn from urban Brazil. We hypothesize that the

specific variant of the receptor gene carried by the individual will alter her risk of depressive symptoms in relation to these social and cultural influences.

Cultural Consonance

While culture is almost universally thought to be an important influence on psychological distress, there exist few research models in which a theoretically explicit concept of culture can be unambiguously linked to a measurement of culture at the individual level, thus making it possible to evaluate the effects of culture relative to other social, psychological, and biological factors. My colleagues and I have proposed just such an approach, referred to as a theory of cultural consonance. In this theory, culture is conceptualized in cognitive terms as a linked series of shared and socially distributed cultural models. The knowledge encoded in cultural models provides a blueprint for what an individual needs to know in order to behave acceptably in a given social setting, and the sharing of these cultural models makes social life possible. We successfully interpret the meaning of others' behaviors based on our shared knowledge of cultural models (D'Andrade 1995).

While many cultural models are widely shared, not all individuals are able to successfully enact each of those cultural models in their own lives. Cultural consonance is the degree to which individuals approximate, in their own beliefs and behaviors, the prototypes for those beliefs and behaviors encoded in shared cultural models. Previous research has shown that low cultural consonance is a stressful experience and is associated with greater psychological distress and higher arterial blood pressure (Dressler 2007).

Recently, in a longitudinal study in urban Brazil, we examined cultural consonance in several domains as predictors of depressive symptoms. We suggested that the degree of cultural consensus in a domain would determine the strength of the effect of cultural consonance in that

domain. We found, as predicted, that cultural consensus around family life was highest among several domains, and, in turn, cultural consonance in family life had the strongest prospective effect on depressive symptoms among the measures of cultural consonance, controlling for the effects of stressful life events (Dressler, et al. 2007). The question now becomes: how might genotype alter this effect of cultural consonance in family life on depressive symptoms?

The Molecular Biology of Depression

With respect to the biology of depression, much attention has been focused on serotonin, a neurotransmitter implicated in the regulation of mood and emotion (Norton and Owen 2005). Genes for various serotonin receptors on neurons have been examined in studies of depression and related conditions, and among these the 2A receptor has received particular attention. A single nucleotide polymorphism in the 2A receptor gene, -1438G/A, is associated with a variety of psychological outcomes. To the best of our knowledge, however, gene-environment interactions have not been investigated with the -1438G/A polymorphism. We hypothesized that the effects of cultural consonance in family life and stressful life events on depressive symptoms over a 2-year period would be modified in the presence of different variants of the 2A receptor gene, controlling for baseline values of these variables and for age, socioeconomic status, and gender.

Methods

This is part of a larger investigation of cultural influences on health in urban Brazil. Research was carried out in the city of Ribeirão Preto, a community of approximately 500,000 people in the northern part of the state of São Paulo. Four neighborhoods representing different socioeconomic levels were selected as sampling strata (Dressler et al. 2007).

Research proceeded in three stages. The first was a stage devoted to the collection of data for cultural domain analyses, culminating in cultural consensus analyses in each of five cultural domains. These data were collected from samples ranging from 15 to 66 respondents, depending on the precise research task, and respondents were purposively selected to represent major dimensions of variation in Brazilian society. The results of the cultural consensus analyses were, in the second stage, used to construct scales of individual belief and behavior, which in turn were used to develop measures of cultural consonance in each domain. These data were collected from 271 respondents in a cross-sectional survey of the four neighborhoods.

The third stage of the study was a 2-year followup study of a subsample of 210 of the original 271 respondents. Fasting blood samples for DNA analysis had been obtained for most respondents, but due to the failure of one kit used to extract DNA from leukocytes, 46 samples were lost. Usable samples of DNA were obtained for 144 of the 210 persons followed up, or 53.1% of the original cross-sectional sample. This represents the sample for the study reported in this paper.

The dependent variable in the research reported here is a Brazilian Portuguese version of the Center for Epidemiologic Studies Depression Scale (CES-D; Cronbach's $\alpha = .88$).

Three covariates are employed: age, gender, and socioeconomic status (SES). SES is assessed as a composite scale of household income, education, and occupational status. A single principal component accounting for 60.7% of the shared variance in these three variables is used as the measure of SES.

Stressful life events were collected using an inventory of events developed and validated in Brazil. This inventory consists of ten major events that are culturally regarded as negative

(such as death of a family member, marital separation, and loss of a job). The number of events occurring in the year prior to the follow-up interview are counted.

As noted, cultural domain analyses provided the basis for the development of measures of cultural consonance. For the cultural domain of the family, we began by asking 43 informants to imagine a family they admired, and to list the characteristics of that family; similarly, we asked them to imagine a family they did not admire, and to list the characteristics of that family. This resulted in two lists of characteristics, each with about 90 terms. After combining synonymous characteristics, we reduced the list to 23 terms, both positive and negative, that we felt reasonably sampled the space of meaning surrounding the family (see Fig. 1).

Next, to explore the structure of the domain, we employed a constrained pile sort, in which we asked informants to first divide the terms into good and bad characteristics of families, and then to further subdivide each of those piles as they wanted. Analyzing the proximity matrix from the pile sort with multidimensional scaling provided a good fit in two dimensions. The MDS appeared to be dominated by a single evaluative dimension ordering family characteristics from good-to-bad, with characteristics at either end of the continuum subdivided qualitatively (see Fig. 2).

In the final step of the cultural domain analysis, we tested for cultural consensus along this evaluative dimension. In order to avoid stacking the deck in favor of cultural consensus, we reduced the number of items to 13, principally by deleting most of the extremely negative characteristics, and had respondents rank these 13 characteristics in order of their importance ‘for having a family.’ There was very high consensus on this dimension of the cultural model of family life, as indicated both by the eigenvalue ratio and by the mean cultural competence (and note that consensus in this domain is highest, Table 1).

Here our interest turned from cultural model to cultural practice. That is, given this agreed-upon cultural model of the family, how do Brazilian families in practice correspond to this shared, prototypical view of the family? To assess this, we developed a measure of cultural consonance in family life. As noted, cultural consonance is the degree to which individuals approximate prototypes for belief and behavior encoded in shared cultural models. This is, if you will, culture actualized. To assess cultural consonance in family life, we generated a series of 18 items as statements about the family. Each subject of each statement was a characteristic derived from the consensus analysis (and we generated more than one statement for several of the more important characteristics). In survey analysis, these became statements of beliefs about, or perceptions of, the respondent's own family. To scale the responses in a way that further linked them to the cultural domain analysis, we weighted each item by the consensus rank of the importance of that characteristic for 'having a family.' This scale has very good internal consistency reliability (see Table 2; the derivation of this scale is described in more detail in Dressler, et al. 2005).

Finally, the identification of the -1438G/A polymorphism was carried out by polymerase chain reaction (PCR). There are three principal variants of the -1438 SNP. In the A/A variant, an individual has two adenine bases paired in the gene on chromosome 13; in the current sample this variant is found in 27.1% of respondents. The G/A variant consists of one adenine base and one guanine base paired, and 45.8% of respondents carry this variant. The G/G variant consists of two guanine bases paired, with 27.1% of respondents carrying this variant (Collier, et al. 1997).

Results

The first step in the analysis was to compare the distributions of variables included in the analysis with the distributions in the larger follow-up sample of 210 and the cross-sectional sample of 271 to determine if the subsample used here was representative of the cross-sectional sample. Goodness of fit tests (Student's *t* and chi-square) indicated no significant differences between the subsample of 144 person used here and either larger sample (see Table 3).

To test the prospective effects of gene-environment interactions on depressive symptoms, an ordinary least squares regression model proposed for longitudinal data by Singer and Willett (2003) was used. The general form of the model is as follows:

$$Y_{\text{time}2} - Y_{\text{time}1} = a + b_1 Y_{\text{time}1} + b_2 X_{\text{time}1} + b_3 X_{\text{time}2 - \text{time}1} + b_4 G_1 + b_5 [(X_{\text{time}2 - \text{time}1}) \times G_1] + e,$$

where 'Y' refers to the dependent variable, 'X' refers to a social or cultural stressor, and 'G' refers to a dichotomous variable representing the presence or absence of a variant for the 2A receptor. In formatting the regression equation in this way, change over time in the dependent variable is examined as a function of change over time in the independent variable, while controlling for initial levels of both independent and dependent variables. The penultimate term is a cross-product representing gene-environment interaction in the regression analysis.

In specifying the regression model, the 2A receptor genotypes were broken into two dummy variables, one indicating the presence-absence of the G/G variant and one indicating the presence-absence of the G/A variant, with the A/A variant serving as the reference category.

Table 4 presents a regression analysis of change in depressive symptoms over time in relation to all variables. The set of interaction effects between genotype and both cultural consonance in family life and stressful life events is significant ($F = 2.45$; $df = 4, 130$; $p = .049$). The occurrence of stressful life events is associated with an increase in depressive symptoms

over the 2-year period and increasing cultural consonance in family life is associated with a decrease in depressive symptoms over that period for persons homozygous for the A/A allele. For persons with either the G/A or the G/G variants, however, those effects are significantly reduced. The pattern of these results is illustrated in Figs. 3 and 4 for cultural consonance in family life and stressful life events, respectively.

Discussion

The results obtained here are consistent with the hypothesis that genotype can alter the impact of cultural consonance and stressful life events on depressive symptoms. Overall, the occurrence of stressful life events and changes in cultural consonance in family life are associated with depressive symptoms; however, these effects are considerably enhanced in the presence of the A/A variant of the -1438G/A polymorphism of the 5HT2A receptor gene. For persons with the G/A or G/G variants, the effects of cultural consonance and stressful life events are muted.

This effect enhancing function of the A/A variant is generalized. When stressful life events occur, it is hypothesized that individuals expend energy in socially readjusting to the changes in their social world brought about by those events. As these changes accumulate, and the energy required to adjust to those changes increases, attempts to adapt can overwhelm the capacity of the individual to change, with deleterious results, including increased depressed affect. This effect is enhanced in the presence of the A/A variant of the 5HT2A gene.

The results of the interaction between genotype and cultural consonance in family life suggest that this effect enhancement can work in both directions. With no change in cultural consonance, the level of depressive symptoms at followup is roughly the same for persons possessing any variant of the serotonin receptor gene. When cultural consonance in family life

increases, depressive symptoms decline more for persons with the A/A variant; when cultural consonance in family life declines, depressive symptoms increase more for persons with the A/A variant. Thus, this polymorphism does not only enhance the deleterious impact of stressful events and circumstances, it also enhances the salutogenic effect of increasing cultural consonance. “Salutogenesis” is a term coined by Antonovsky to describe the opposite of the effects of stressors, i.e., experience in the social world that leads to better health.

For many candidate genes, the biological action of the gene is not well-understood. For the 2A receptor gene, however, there is some intriguing evidence of its effects. Under conditions of stress, there is an increase in serotonin receptors in the frontal cortex of the brain, relative to the brain stem. In research on cell lines, messenger RNA (mRNA) activity is enhanced in the presence of the A/A genetic variant, relative to the other variants. Roughly speaking, this suggests that for persons possessing the A/A variant, there might be greater information throughput in the frontal cortex during times of heightened arousal. This may in turn enhance the effects of changes in culturally salient social relationships on mood (Dwivedi, et al. 2005; Parsons, et al. 2004).

The longitudinal design and data-analytic model also enable us to compare baseline effects of cultural consonance with change over time. Over the 2-year follow-up, as respondents perceived their families to become more like the cultural prototype of the family, their reported depressive symptoms declined, especially if they had the A/A variant of the 5HT2A gene. At the same time, baseline, and presumably longer term, achievement of the cultural ideal was not moderated by genotype, suggesting that the achievement of this cultural ideal in and of itself leads to lower depressive symptoms. Given the importance of the family as an institution in Brazilian society, it is not surprising that long-term difficulties in achieving collective

expectations in this sphere of life would be stressful and demoralizing for individuals, regardless of their genetic background (da Matta 1985).

In conclusion, these results suggest that there is an active synergism between an individual's genetic background and where that individual is situated in a social space defined by shared cultural meaning. This is certainly one example of a biocultural process.

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Fig. 1

União - Union
Uma família que briga – A family that fights
Bom relacionamento – Good relationships
Desrespeito - Disrespect
Amor - Love
Tem vícios – A family with members that have addictions
Religiosa - Religious
Se ajudam – Help one another
Sem educação – Lacking manners
Honestidade - Honesty
Violência - Violence
Falsidade - Pretence
Uma família com firmeza – Strength to confront problems
Fazem críticas - Critical
Trata bem os outros – Treat people well
Egoísmo – Self-centeredness
Família alegre - Happiness
Família trabalhadora – Hard-working
Família com diálogo - Communications
Compreensão - Understanding
Irresponsabilidade - Irresponsibility
Infidelidade - Unfaithfulness
Exploração - Exploitation
Família organizada - Organized

Cultural Modeling - The Domain of Family Life

Fig. 2

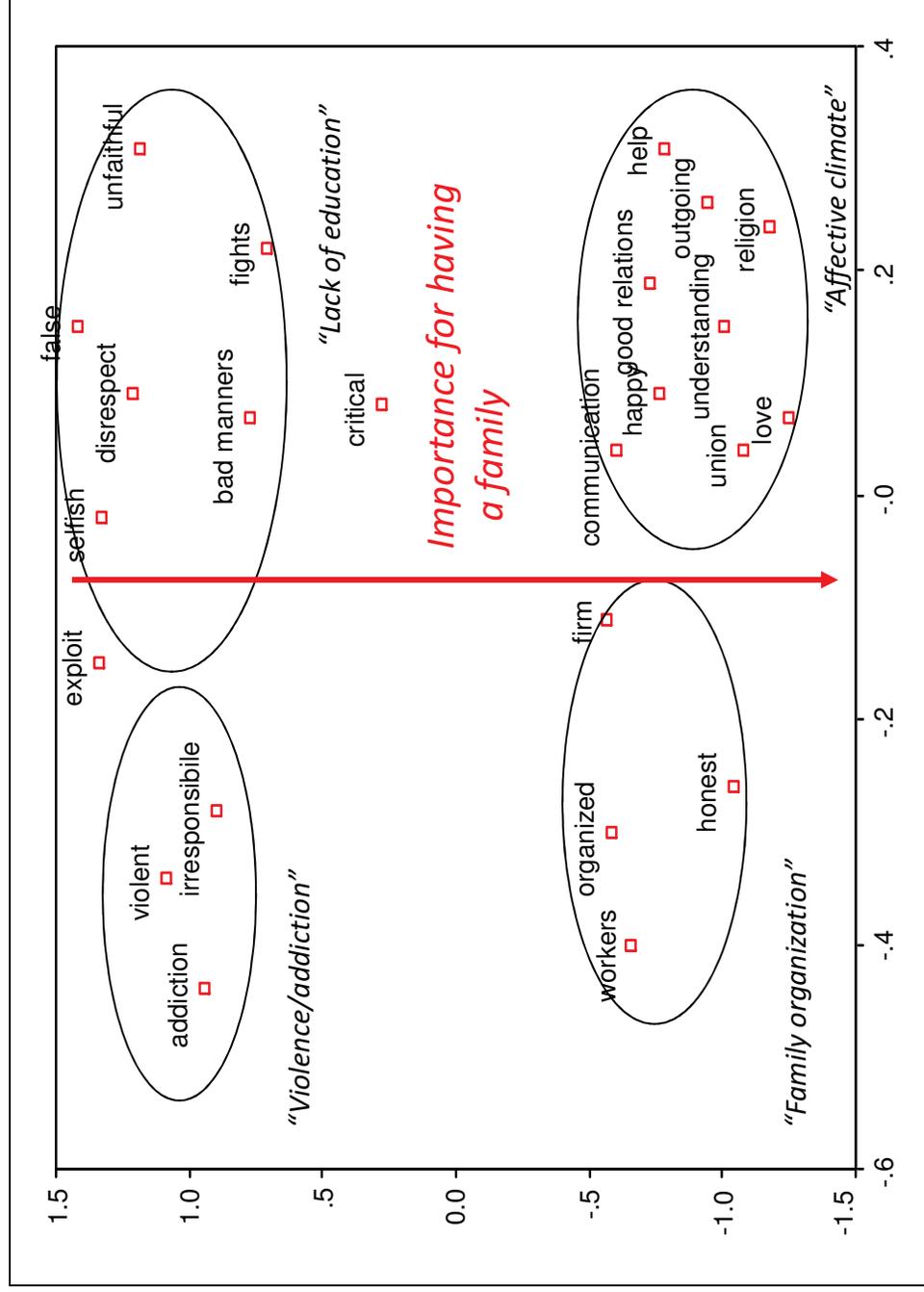


Table 1: Consensus results – Social factors

Domain:	Eigen-value ratio	Mean competence	S.D. competence	Competence range
--Social support	6.53	.67	.14	.25-.92
--Lifestyle (Material goods) (Leisure)	6.59 (5.99) (4.64)	.71 (.76) (.66)	.12 (.11) (.21)	.43-.86 (.44-.93) (.09-.89)
--Family life	7.42	.82	.09	.63-.93
--National char.	3.97	.57	.19	.22-.90 (1 negative)

Table 2: Scale of Cultural Consonance in Family Life

	Item-total correlation	Mean (range 0-3)	Std. Deviation
Feel close to one another	.45	2.50	.79
Family should be organized*	.32	2.15	.96
Don't have help*	.35	1.04	.88
Family are hard workers	.32	2.70	.52
We avoid one another*	.69	.86	.92
Wish for more love in family*	.49	1.62	1.09
We are well-adjusted	.66	2.05	.82
Act without thinking of family	.22	.76	.83
Family too critical	.54	1.08	.80
Family confronts problems	.46	2.26	.79
Mine is happy family	.61	2.31	.73
We understand each other	.71	2.17	.80
We help each other	.61	2.33	.75
Don't have time to listen*	.46	1.05	.89
Don't have enough respect	.66	.82	.82
We talk about important things	.62	2.32	.72
Feel love for one another	.67	2.38	.69
Wish didn't fight so much	.41	1.45	1.08

*Item reverse coded

Cronbach's alpha = .868

Table 3: Comparison of three samples

Variable:	Current study (n=144)	Total followup (n=210)	Total cross-sectional (n=271)
Depressive symptoms	12.4 (± 10.4)	12.4 (± 10.1)	12.5 (± 10.1)
Age	40.5 (± 11.3)	40.6 (± 11.3)	40.5 (± 11.6)
Sex (% female)	61.8	63.3	60.9
SES	0.012 (± 0.99)	0.012 (± 1.01)	0.00 (± 1.00)
Cultural consonance in family life (time 1)	107.6 (± 24.1)	106.5 (± 24.8)	106.9 (± 24.6)
Stressful life events	2.1 (± 1.68)	2.2 (± 1.72)	--

Table 4: Regression analysis of gene x culture interaction

Variable:	Model 1	Model 2	Model 3
Age	.010	.005	.056
Gender	-.141*	-.145**	-.150**
SES	.022	.019	-.029
Depression _{time1}	-.581***	-.585***	-.595**
CCFL _{time1}	-.213***	-.219***	-.184*
CCFL _{time2 - time1}	-.284***	-.280***	-.469***
Stressful life events	.161**	.154**	.399***
5HT2A G/A	-	-.039	.169
5HT2A G/G	-	-.087	.137
G/A x CCFL _{time2 - time1}	-	-	.227**
G/G x CCFL _{time2 - time1}	-	-	.163*
G/A x Stressful life events	-	-	-.277*
G/G x Stressful life events	-	-	-.317**
Multiple R	.609***	.613***	.648***
Multiple R ²	.371	.376	.420

Fig. 3: Change in depressive symptoms in relation to cultural consonance in family life and stressful life events, by genotype

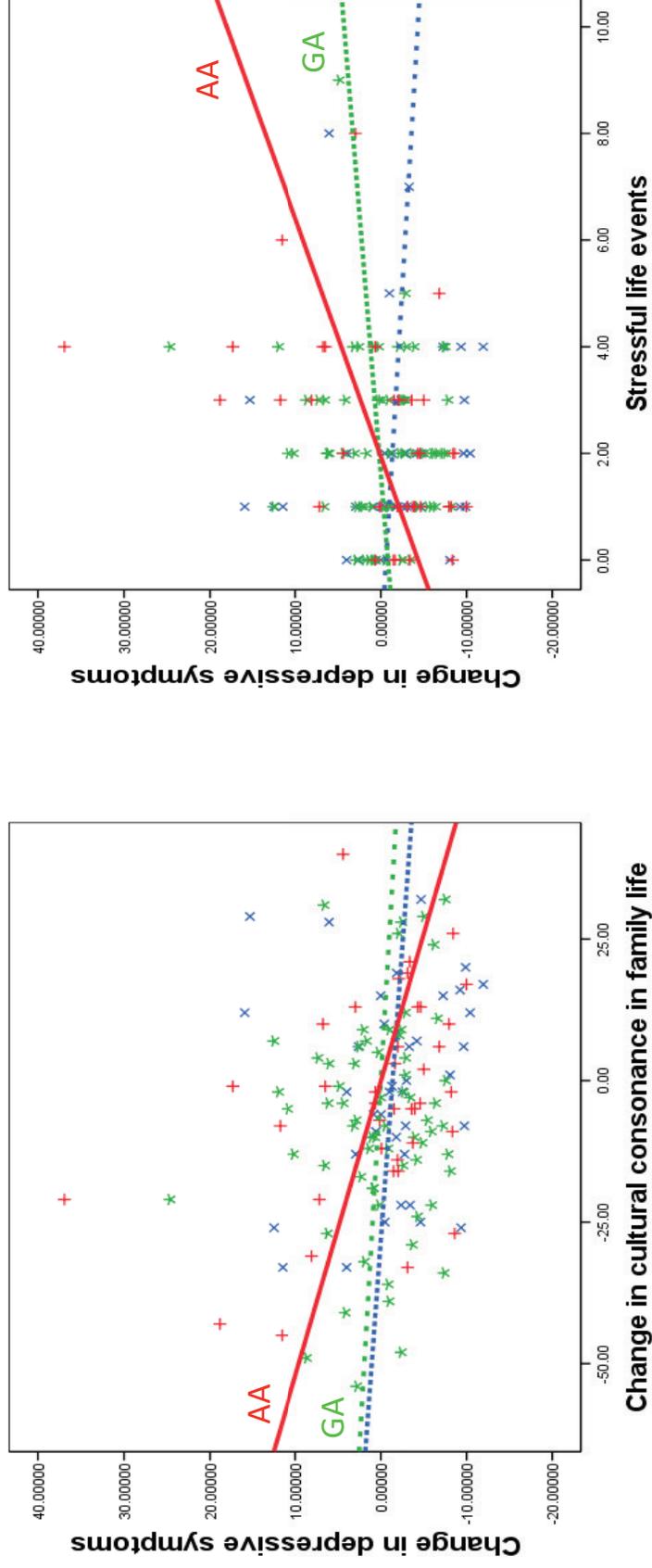


Fig. 4: Longitudinal Change in Depressive Symptoms and Cultural Consonance in Family Life by Serotonin 2A Receptor Polymorphism

