

The Influence of Urban/Rural Residency on Depressive Symptoms is Moderated by the Serotonin Receptor 2A Gene

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Gene–environment interactions are thought to be involved in the development of depression. Here we examined the interaction effect between urban/rural residency and the serotonin receptor 2A (HTR2A) gene on subclinical depressive symptoms. The participants were 1,224 Finnish men and women being followed in the on-going population-based study of “Cardiovascular Risk in Young Finns”. Urban/rural residency was determined on the basis of a (1) subjective report and (2) the population density of the residential area. Depressive symptoms were measured in two test settings four years apart. There was a significant gene–environment interaction, such that the urban residency was associated with low depressive symptoms in individuals carrying the T/T or T/C genotype of the T102C polymorphism, but not in those carrying the C/C genotype. The T allele was associated with high depressive symptoms in remote rural areas, but with low depressive symptoms in urban or suburban areas. The gene–environment interaction was not accounted by level of education, social support, unemployment, or partnership status. The HTR2A gene may be involved in the development of depression by influencing how individuals respond to environmental conditions. © 2007 Wiley-Liss, Inc.

KEY WORDS: HTR2A; gene–environment interaction; neighborhood; depression

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INTRODUCTION

Major depressive disorder is estimated to affect 7–11% of people at some point in life [Ayuso-Mateos et al., 2001], and subclinical depressive symptoms may be even more prevalent [Judd et al., 2002b]. Some studies have reported the prevalence of depression to be higher in urban than in rural areas [Blazer et al., 1985; Paykel et al., 2000; Sundquist et al., 2004], suggesting that socioregional factors may be involved in the development of depression. However, other studies have failed to demonstrate an urban–rural gradient in mental health [Romans-Clarkson et al., 1990; Lehtinen et al., 2005]. These inconsistent results suggest that the influence of socioregional factors is likely to vary by society and population [see Verheij, 1996; Judd et al., 2002a for reviews].

The mechanisms mediating the potential depressogenic influence of an urban living have not been identified, although a variety of candidates have been considered [Verheij, 1996]. Urban residents may experience more stressful life events [Paykel et al., 2000], while rural residents are often assumed to have more cohesive social networks that protect them from psychosocial stressors [Romans-Clarkson et al., 1990; Sundquist et al., 2004]. Regional differences in marital status, education, and unemployment have also been suggested to play a role [Verheij, 1996].

Urban and rural regions are likely to have both positive and negative qualities, and the relative impact of these qualities may be dependent on individual characteristics [Verheij, 1996]. Recent research has demonstrated that genetic factors may influence how individuals respond to their environment. For example, the serotonin transporter gene 5-HTTLPR polymorphism has been found to moderate the impact of negative life events on mental and physical health [Caspi et al., 2003; Eley et al., 2004; Grabe et al., 2005; Kendler et al., 2005], such that individuals carrying the “short” allele of the 5-HTTLPR are more vulnerable to environmental stressors.

In the present study we examined whether the T102C polymorphism of the serotonin receptor 2A gene (HTR2A) moderated the association between urban/rural residency and depressive symptoms in a population-based sample of Finnish men and women. The HTR2A gene may be involved in the development of depression because the binding potential of the 5-HT_{2A} receptors in the brain is associated with depression and suicidal behavior [van Heeringen et al., 2003] and related personality traits [Moresco et al., 2002]. The T102C polymorphism of the HTR2A gene, in turn, has been associated with the density of 5-HT_{2A} receptors in the brain [Turecki et al., 1999; Poleskaya and Sokolov, 2002], and the C allele of the T102C polymorphism has been associated with depression and suicidal behavior [Du et al., 2000]. However, several studies have failed to replicate this finding [see Anguelova et al., 2003],

and some studies have found the presence of the T rather than of the C allele to confer a risk for depression [Eley et al., 2004].

Previous studies carried out in Finland [Lehtinen and Joukamaa, 1994; Lehtinen et al., 2005] have found no differences in the prevalence of depression between rural and urban regions, suggesting a homogenous distribution of depressogenic influences across the Finnish urban–rural continuum. Although studies in other countries have generally found higher depression in urban than rural areas [Blazer et al., 1985; Paykel et al., 2000], one could expect the association, if any, to be the opposite in Finland. From 1960s onwards an increasing number of people have been moving from rural regions to city centers, which has contributed to a decline of the social and economic structures of the rural areas. Compared to urban areas, the remote rural areas are nowadays characterized by, among other factors, lower socioeconomic status (SES); higher morbidity, suicide rates, and prevalence of substandard housing; and fewer opportunities for employment [Kainulainen et al., 2001; Karvonen and Rintala, 2004]. Given that social and economic hardships are known to be associated with poorer mental health [Lorant et al., 2003], rural residency can be hypothesized to confer an increased risk of the development of depressive symptoms.

In sum, we hypothesized that rural residency is associated with higher depressive symptoms, and that this association is moderated by the HTR2A gene, such that individuals carrying C alleles of the T102C polymorphism are more prone to the depressogenic influence of rural residency. We also assessed if education level, unemployment, marital status, or perceived social support accounted for the potential association between urban/rural residency and depressive symptoms.

MATERIALS AND METHODS

Participants

The participants were 1,224 men and women participating in the on-going population-based study of “Cardiovascular Risk in Young Finns” [Åkerblom et al., 1991]. In this study, a randomly selected sample of 3,596 Finnish healthy children and adolescents from six birth cohorts (aged 3–18 years at the baseline) has been followed since 1980. Complete details of the sample are given elsewhere [Åkerblom et al., 1991]. In the present study, a subsample of 1,593 participants was derived for genotyping at random from the original sample, and depending on the variables used 1,185–1,224 had complete data. The study was approved by local ethics committees, and all participants gave their written informed consent and gave blood samples in accordance with the Helsinki Declaration.

Measures

The measures used in the present study were applied in the 5th and 6th follow-up phase (17 and 21 years after the baseline, referred to as Year 17 and Year 21), when the participants were 20–35 and 24–39 years of age, respectively.

Depressive symptoms were assessed in Year 17 and Year 21 using a modified version of Beck’s Depression Inventory (BDI) [Beck and Steer, 1987; see Katainen et al., 1999]. In the original version of the BDI, individuals are asked to choose one of the four alternative response statements, representing ascending levels of symptom severity, in each of the 21 items. In the modified version used here, the 21 items of the scale were the second mildest statements of the original BDI items (e.g., “I often feel sad”). The participants were asked to rate each of the 21 statement items on a five-point scale ranging from totally disagree (1) to totally agree (5), and the depressive symptoms score was calculated as the sum of these 21 items. The second

mildest statements of the original BDI items were selected for the modified scale because they were expected to most accurately measure individual differences in depressive symptoms in a normal population [see Katainen et al., 1999]. The Cronbach’s alpha reliabilities for depressive symptoms were $\alpha > 0.90$.

Urban/rural residency was determined on the basis of two indicators in Year 21. The participants reported on a four-point scale whether they were currently living in (1) a remote rural area (i.e., low-density rural region), (2) a rural area (e.g., rural town), (3) a suburban area, or (4) a city. This measure of urban/rural residency will be referred to as “place of residence.”

Urban/rural residency was also assessed by the population density of the municipality in which the participant was living. Population density data were obtained from the database of Statistics Finland, and expressed as the number of inhabitants per square kilometer of land. This measure of urban/rural residency will be referred to as “population density.” Note that “place of residence” refers to more local characteristics of residence than “population density”, and that different kinds of local residential areas may exist in a given municipality (e.g., a remote rural area within a high density municipality). In Year 21 the participants were living in 227 different municipalities around Finland.

Information on the participants’ residency was not obtained in the Year-17 follow-up phase. However, in Year 21 the participants provided information on their migration history, from which it was possible to determine their home municipality in Year 17. Urban/rural residency for the Year 17 was therefore measured only on the basis of the population density of the municipality.

Level of education was assessed on the basis of years of completed education in Year 21.

Social support was assessed in Year 21 using the Perceived Social Support Scale Revised (PSSS-R) devised by Blumenthal et al. [1987]. The 12 items of the PSSS-R dealing with perceived support from family, friends, and significant other(s) were rated on a five-point scale ranging from totally disagree (1) to totally agree (5). The Cronbach’s alpha reliability for social support in the CRYF sample was $\alpha > 0.90$.

Partnership status was coded as a dichotomous variable (1 = married or cohabiting; 2 = not living with a partner). Data on partnership status was available for Year 21, but not for Year 17.

Unemployment status was also coded as a dichotomous variable (1 = unemployed, 2 = employed/student/other). Data on unemployment was available for Year 21, but not for Year 17.

HTR2A 102 T > C Genotyping

Genomic DNA was extracted from peripheral blood using a commercially available kit (Qiagen Inc., Hilden, Germany). DNA samples were genotyped by employing the 5’ nuclease assay and fluorogenic TaqMan MGB probe [Livak, 1999] using the ABI Prism 7900 HT Sequence Detection System (Applied Biosystems, Foster City, CA). The nucleotide sequences of primers and allele-specific probes, labeled with the reporter dyes FAM or VIC, were deduced from sequences deposited in the GenBank database and synthesized in conjugation with Applied Biosystems using the TaqMan® Validated SNP Genotyping Assay (SNP rs6313, assay ID: C-3042197-1). PCR reaction containing genomic DNA, 1× Universal PCR Master Mix, 900 nM of each primer, and 200 nM of each probe was performed in 96-well plates using the standard protocol in a total volume of 25 μ l. After PCR amplification, the endpoint reading of the fluorescence signal generated from each probe was measured by the allelic discrimination analysis module, resulting in clear identification of three genotypes.

TABLE I. Descriptive Statistics (n = 1,224)

Variable	n (%)	Mean (SD)
Age		31.8 (5.1)
Gender		
Women	672 (55.0)	
Men	552 (45.0)	
HTR2A		
T/T	129 (10.5)	
T/C	538 (44.0)	
C/C	557 (45.5)	
Place of residence		
Remote rural	193 (15.8)	
Rural	226 (18.5)	
Sub-urban	560 (45.7)	
Urban	245 (20.0)	
Year-21 population density		94.4 ^a
Year-17 depressive symptoms		44.1 (13.7)
Year-21 depressive symptoms		42.5 (13.8)
Social support		67.5 (12.5)
Years of education		14.7 (3.0)
No partner	379 (31.4)	
Unemployed	69 (5.7)	

^aMedian value of the nontransformed population density (person/km²).

Data Analysis

The main effects of place of residence (four levels: remote rural, rural, suburban, and urban), the HTR2A gene (three levels: T/T, T/C, C/C) and their interaction were assessed with analysis of covariance (for continuous variables, controlling for age and gender) and with chi-square tests (for discrete variables). The main effects of population density and its interaction effect with the HTR2A gene were assessed with linear (for continuous variables) and logistic (for discrete variables) regression analysis, with age and gender as covariates. The population density was unevenly distributed and was therefore divided into deciles, and this regressor was used in the analyses. In the regression analyses, the HTR2A gene was coded as a continuous regressor indicating the number of C alleles (T/T = 0, T/C = 1, C/C = 2).

RESULTS

Main Effects

Descriptive statistics for the sample are shown in Table I. The HTR2A gene was not associated with depressive symptoms in Year 17 ($P=0.61$) or Year 21 ($P=0.42$), with place of residence ($P=0.67$) or with population density ($P=0.17$). Place of residence was not associated with depressive symptoms, although there was a tendency for individuals in remote rural areas to have higher depressive symptoms than those from other areas (Table II). Individuals in remote rural areas had lower social support, while those living in more urban areas had higher levels of education and were more likely to be living without a partner (Table II).

TABLE II. Year-21 Study Variables by Place of Residence

	Remote rural	Rural	Suburban	Urban	<i>P</i>
Depressive symptoms (M ± SD)	44.24 (14.64)	42.54 (13.85)	42.36 (13.36)	41.62 (14.00)	0.277 ^a
Social support (M ± SD)	63.48 (14.48)	68.70 (11.02)	68.03 (12.39)	68.13 (11.92)	<0.001 ^a
Not living with a partner (%)	20.47	20.14	27.86	51.68	<0.001 ^b
Unemployed (%)	5.51	3.60	6.53	4.33	0.239 ^b
Years of education (M ± SD)	13.62 (2.75)	14.01 (2.61)	14.76 (3.08)	15.79 (3.10)	<0.001 ^a

^aAnalysis of variance.

^bChi square test.

The Spearman's rank correlation coefficient between place of residence and Year-21 population density was $r=0.60$ ($P<0.001$). There was a tendency for higher population density to be associated with lower depressive symptoms in Year 21 (Year 21: $b=-0.24$, $SE=0.14$, $\beta=-0.05$, $P=0.08$; Year 17: $b=-0.17$, $SE=0.14$, $\beta=-0.04$, $P=0.25$). Population density was associated with higher social support in Year 21 ($b=0.36$, $SE=0.12$, $\beta=0.08$, $P<0.01$) but not in Year 17 ($b=0.03$, $SE=0.12$, $\beta=0.01$, $P=0.81$), and with higher education level (Year 21: $b=0.22$, $SE=.03$, $\beta=0.20$, $P<0.001$), higher likelihood of having no partner (Year 21: $OR=1.08$ (95% $CI=1.04-1.13$), $P<0.001$), and marginally associated with lower likelihood of being unemployed (Year 21: $OR=0.93$ (95% $CI=0.86-1.01$), $P=0.07$).

Gene-Environment Interactions

The interaction effect between the HTR2A gene and place of residence was statistically significant ($F=2.13$, $df=6$, 1,210; $P=0.05$; Fig. 1) and showed that the higher level of urbanicity was associated with lower depressive symptoms in individuals carrying the T/T or T/C genotype (linear contrast $P<0.01$, magnitude of effect $\eta^2=0.01$), but not in those carrying the C/C genotype ($P=0.49$). The T allele was associated with lower depressive symptoms among individuals living in urban or suburban areas (linear contrast $P=0.01$, $\eta^2=0.01$), but with higher depressive symptoms among those living in remote rural areas (linear contrast $P=0.03$, $\eta^2=0.03$; Fig. 1).

The interaction effect between HTR2A and Year-21 population density was significant when predicting Year-21 depressive symptoms ($b=0.59$, $SE=0.21$, $P<0.01$) and showed that high population density was associated with low depressive symptoms in individuals carrying the T/T or T/C genotype ($b=-0.51$, $SE=0.20$, $\beta=-0.10$, $P=0.01$), but not in those carrying the C/C genotype ($b=0.08$, $SE=0.20$, $\beta=0.02$, $P=0.69$).

The interaction effect between the HTR2A and Year-17 population density was not statistically significant when

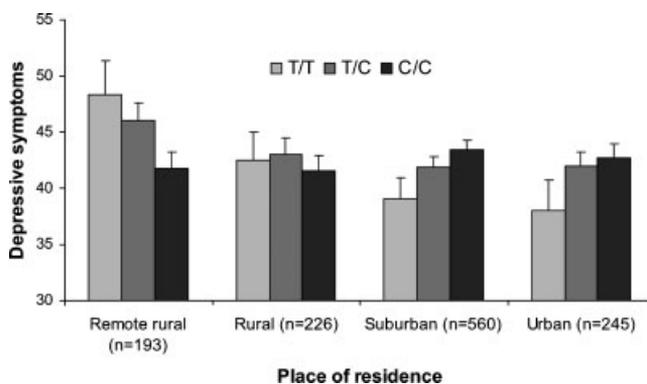


Fig. 1. Depressive symptoms by place of residence and HTR2A genotype group.

predicting depressive symptoms in Year 17 ($b = 0.22$, $SE = 0.22$, $P = 0.33$), although it was in the same direction as the interactions above (T/T or T/C genotype: $b = -0.28$, $SE = 0.20$, $\beta = -0.06$, $P = 0.17$; C/C genotype: $b = 0.04$, $SE = 0.21$, $\beta = 0.01$, $P = 0.86$). The HTR2A \times Year-17 population density interaction effect was significant when predicting depressive symptoms in Year 21 ($b = 0.50$, $SE = 0.21$, $P = 0.02$), and showed that high Year-17 population density predicted low Year-21 depressive symptoms in carriers of the T/T or T/C genotypes ($b = -0.56$, $SE = 0.19$, $\beta = -0.11$, $P < 0.01$) but not in carriers of the C/C genotype ($b = 0.00$, $SE = 0.20$, $\beta = 0.00$, $P = 0.99$).

Finally, we examined whether controlling for social support, unemployment, marital status, or level of education affected the interaction effect between HTR2A gene and urban/rural residency on depressive symptoms in Year 21. Whether entered individually or all at the same time in the model, the control variables did not significantly alter the statistical significance of the interaction effect in any of the models (data not shown). When predicting depressive symptoms in Year 21 with all the control variables incorporated into the model, the HTR2A \times place of residence was still marginally significant ($F = 2.05$; $df = 6, 1,180$; $P = 0.06$) and the HTR2A \times Year-21 population density interaction effect was significant ($b = 0.49$, $SE = 0.20$, $P = 0.01$).

DISCUSSION

The present study examined the variation of depressive symptoms on the basis of urban/rural residency and the serotonin receptor 2A (HTR2A) gene in a population-based sample of Finnish adults. We found that when individuals were not stratified by their genotype, there was only a nonsignificant tendency for higher urbanicity to be associated with lower depressive symptoms. However, when examined by genotype groups, urban residency was associated with lower depressive symptoms in individuals carrying the T/T or T/C genotype of the T102C polymorphism of the HTR2A gene, while this was not true for individuals carrying the C/C genotype. The direction of the allelic association between the T102C polymorphism and depressive symptoms was the opposite in urban and suburban areas as opposed to remote rural areas, such that the T allele was associated with low depressive symptoms in the urban and suburban areas but with high depressive symptoms in remote rural areas.

Urban/rural residency was determined on the basis of a self-report and an objective measure (i.e., population density), both of which provided evidence for the HTR2A–urbanicity interaction. Depressive symptoms were measured in two test settings taken 4 years apart. The HTR2A–urbanicity interaction effect was significant in the three analyses predicting depressive symptoms in Year 21, but was not significant in the one analysis predicting depressive symptoms in Year 17. However, the nonsignificant interaction was in the same direction as the significant ones. Additional studies, especially in countries where the urban–rural difference in depression is greater than in Finland, should be conducted to further evaluate the robustness of the present results. Further research is also needed to identify the mechanisms involved in the HTR2A-dependent regional differences, which were not accounted by social support, unemployment, level of education, or marital status.

Depressive symptoms tended to be higher and perceived social support was lower in remote rural areas than in urban areas. This supported our hypothesis that in Finland urban residency may provide more opportunities for psychosocial well being than the residency in remote rural areas, although the regional differences were small. Individuals carrying the T/T or T/C genotype of the T102C polymorphism may be more

sensitive to these environmental conditions than those carrying the C/C genotype. Perhaps the T-allele carriers are more able to take advantage of the urban opportunities, but are also more vulnerable to their lack. This might be mediated by anxiety sensitivity, which has been associated with the 5-HT_{2A} receptors [Moresco et al., 2002; Weisstaub et al., 2006]. The 5-HT_{2A} receptors have also been implicated in the functioning of the prefrontal cortex [van Heeringen et al., 2003; see Deakin, 1996] which is involved in cognitive control and emotion regulation [Miller, 2001; Ochsner et al., 2002]. These factors might also play a role in the differential responsiveness to environmental circumstances.

Community-level factors may provide valuable information on how environmental context affects biological processes, though they remain less studied than individual-level variables. Twin and family studies have demonstrated that socioregional factors such as urban/rural residency may influence the expression of heritable tendencies related to alcohol use [Dick et al., 2001], criminality [Christiansen, 1977; cited in Raine, 2002], and schizophrenia [Van Os et al., 2003]. A recent study [Manuck et al., 2005] found low neighborhood SES to predict low serotonin functioning even when the participant's own SES was taken into account. The present study adds to this literature by showing that the direction of the association between a polymorphism and a phenotype of interest may even be the opposite in different social environments. Interestingly, Comings and MacMurray [2006] have reported a similar reversal of genetic effect, which they termed genostasis, in a study of dopamine receptor gene DRD1, maternal age at birth, and psychiatric disorders.

In a previous study [Jokela et al., 2007] with the same sample as here we found that the HTR2A gene moderated the association between exposure to maternal nurturance in childhood or adolescence and depressive symptoms in adulthood, such that high maternal nurturance predicted low depressive symptoms in individuals carrying the T/T or T/C genotypes, but not in those carrying the C/C genotype. Together our two studies suggest that the HTR2A gene may influence how responsive individuals are to early experiences and current environmental conditions.

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