ORIGINAL ARTICLE

Serotonin Receptor 2A Gene and the Influence of Childhood Maternal Nurturance on Adulthood Depressive Symptoms

Markus Jokela, MA, MSocSc; Liisa Keltikangas-Järvinen, PhD; Mika Kivimäki, PhD; Sampsa Puttonen, PhD; Marko Elovainio, PhD; Riikka Rontu, PhD; Terho Lehtimäki, MD, PhD

Background: Gene–environment interactions are assumed to be involved in the development of depression.

Objective: To determine whether the serotonin receptor 2A (*HTR2A*) gene moderates the association between childhood maternal nurturance and depressive symptoms in adulthood.

Design: A 21-year, prospective, longitudinal study with 2 measurements of the independent and dependent variables.

Setting: A population-based sample.

Participants: A subsample of 1212 participants of the Cardiovascular Risk in Young Finns study, aged 3 to 18 years at baseline.

Main Outcome Measure: Depressive symptoms in adulthood.

Results: Individuals carrying the *T/T* or *T/C* genotype of the T102C polymorphism of the *HTR2A* gene were responsive to the protective aspects of nurturing mothering, so that in the presence of high maternal nurturance, they expressed low levels of depressive symptoms, while this was not true with the carriers of the *C/C* genotype.

Conclusion: The *HTR2A* gene may be involved in the development of depression by influencing the ability of individuals to use environmental support.

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Author Affiliations: Department of Psychology, University of Helsinki (Mr Jokela and Drs Keltikangas-Järvinen, Kivimäki, Puttonen, and Elovainio), and Finnish Institute of Occupational Health (Dr Kivimäki), Helsinki; and Laboratory of Atherosclerosis Genetics, Tampere University Hospital, and Centre for Laboratory Medicine and Department of Clinical Chemistry, Medical School, University of Tampere, Tampere (Drs Rontu and Lehtimäki), Finland.

DEPRESSION IS ONE OF THE leading causes of mental and psychological disability; according to recent estimates, depression will account for 15% of the disease burden worldwide by 2020.[1] The current view of depression emphasizes the importance of gene–environment interactions in the development of depression.[2] Evidence indicates that vulnerability to depression is influenced by early life experiences, such as the relationship with the primary caregiver.[3,4] Studies[5] on nonhuman primates suggest that the effects of early rearing conditions may be influenced by genetic background. For instance, allelic variation in the serotonin transporter gene has been found to moderate the harmful effects of deleterious rearing circumstances.[6] Likewise, Caspi et al[7] found that childhood maltreatment increased the risk of adult depression among individuals carrying a "short" allele of the serotonin transporter gene polymorphism but not among those carrying 2 "long" alleles. The impact of maltreatment on the development of antisocial behavior also has been shown to depend on genetic background.[8,9]

It is likely that other serotonergic genes besides the serotonin transporter gene are involved in gene–environment interactions related to depression, although they have been studied less. The serotonin receptor 2A (*HTR2A*) gene is considered to be a candidate gene for depression because the binding potential of the serotonin 2A receptors is associated with depression and suicidal behavior[10] and related traits.[11] The *C* allele of the *HTR2A* T102C polymorphism has been associated with depression and suicidal behavior,[12] although several studies[13] have failed to replicate these findings and some studies[14] have found the presence of the *T* rather than of the *C* allele to confer a risk for depression. Owing to the inconsistency of the findings of these genetic studies, it is reasonable to hypothesize that the behavioral expression of the *HTR2A* gene may be conditional on environmental exposure, thus confounding genetic associations.

Molecular and psychological perspectives suggest the existence of gene–parenting interactions. Research[15] on nonhuman animals indicates that parental care may alter the expression of genes. In addition, gene–environment interactions are assumed to be ubiquitous in the process

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of socialization,[16] but the empirical evidence for this assumption is limited. In the present study, we examined whether the common variation in the *HTR2A* T102C polymorphism moderated the association between childhood and adolescent parental care and adulthood depressive symptoms. We hypothesized that individuals carrying the putative risk allele (102C) are more prone to negative environmental influences than their *T* allele–carrying counterparts.

METHODS

The subjects were derived from the Cardiovascular Risk in Young Finns study.[17] In this prospective epidemiological study, a randomly selected sample of 3596 Finnish healthy children and adolescents from 6 birth cohorts (aged 3-18 years at baseline) has been followed up since 1980, focusing on the development of risk factors of coronary heart disease. In the present study, a subsample of 1593 participants was selected at random for genotyping and, depending on the variables included in the analysis, 820 to 1212 had complete data. All the subjects gave their written informed consent and gave blood samples in accordance with the Declaration of Helsinki.

ASSESSMENT OF MATERNAL NURTURANCE

Maternal nurturance was self-rated by the mothers of the subjects using a scale derived from the Operation Family study,[18] addressing the emotional significance of the child for the mother. The scale comprises 4 items ("My child is emotionally important to me," "I enjoy spending time with my child," "I am emotionally important to my child," and "My child allows/enables me to fulfill myself"), which were rated on a 5-point scale ranging from totally disagree (1) to totally agree (5). The assessments were made at baseline (referred to as year 0, subjects being aged 3, 6, 9, 12, 15, and 18 years) and 3 years after baseline (year 3, subjects being aged 6-21 years). The Cronbach α reliabilities for year 0 and year 3 nurturance were $\alpha=.66$ and $\alpha=.78$, respectively, and the 3-year test-retest Pearson product moment correlation was $r=0.37$ ($P<.001$) ($r=0.52$ after correction for attenuation because of measurement error). The nurturance variable was negatively skewed and was corrected by a cubic root transformation.

ASSESSMENT OF DEPRESSIVE SYMPTOMS

Depressive symptoms were assessed with a modified version of the Beck Depression Inventory[19] and self-rated by the subjects. In the original version of the Beck Depression Inventory, subjects are asked to choose 1 of the 4 alternative response statements in each of 21 items. In the modified version used herein, the subjects were asked to rate each of the 21 items (eg, "I often feel sad") on a 5-point scale ranging from totally disagree (1) to totally agree (5). These items were the second mildest statements of the original Beck Depression Inventory items, and were selected because they were expected to most accurately measure individual differences in depressive symptoms in a healthy population.[20] The revision made the inventory less time-consuming and easier to fill out. Assessments of depressive symptoms were made 17 and 21 years after baseline (at year 17, the age range was 20-35 years; and at year 21, 24-39 years). The Cronbach α reliabilities for year 17 and year 21 depressive symptoms were $\alpha=.89$ and $\alpha=.90$, respectively, and the 4-year test-retest Pearson product moment correlation was $r=0.66$ ($P<.001$) ($r=0.73$ after correction for measurement error).

HTR2A 102 *T*>*C* (34 S/S) GENOTYPING

Genomic DNA was extracted from peripheral blood using a commercially available kit (Qiagen Inc, Hilden, Germany). DNA samples were genotyped by using the 5′ nuclease assay and a fluorogenic probe (TaqMan MGB)[21] using a detection system (ABI Prism 7900HT Sequence Detection System; Applied Biosystems, Foster City, Calif). 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 an assay (TaqMan Validated SNP Genotyping Assay; single nucleotide polymorphism rs6313, assay C-3042197-1). A polymerase chain reaction containing genomic DNA, 1×Universal PCR Master Mix, 900nM of each primer, and 200nM of each probe was performed in 96-well plates using the standard protocol in a total volume of 25 µL. After polymerase chain reaction amplification, end point reading of the fluorescence signal generated from each probe was measured by the allelic discrimination analysis module, resulting in clear identification of 3 genotypes.

DATA ANALYSIS

An analysis of covariance, with sex and age as covariates, was used to assess the main effects of the *HTR2A* gene on depressive symptoms and maternal nurturance. Multiple regression analysis was used to assess the association of the *HTR2A* gene (coded as a continuous variable, where *T/T* indicates 0; *T/C*, 1; and *C/C*, 2), maternal nurturance, and their interaction on depressive symptoms, with sex and age as covariates. We tested 9 (3×3) separate regression models involving the *HTR2A* gene and maternal nurturance at year 0 and year 3 and the mean of those scores as independent variables, and depressive symptoms at year 17 and year 21 and the mean of those scores as dependent variables. Herein, the results for the 3 regression models with the mean depressive symptom scores as the dependent variable are presented (945, 834, and 820 for year 0, year 3, and mean nurturance, respectively). The results were similar and significant when year 17 and year 21 depressive symptoms were used as the dependent variables (938-1212; data available from the authors on request).

RESULTS

ANALYSES OF MAIN EFFECTS

The descriptive statistics for the sample are presented in **Table 1**. The *HTR2A* gene had no main effect on depressive symptoms (**Table 2**), and it was not related to maternal nurturance ($P>.68$ for all). Year 3 and mean maternal nurturance were associated with lower levels of depressive symptoms (year 0 nurturance: $b=-1.67$, $SE=1.34$, $\beta=-.04$, $P=.22$; year 3 nurturance: $b=-3.42$, $SE=1.20$, $\beta=-.10$, $P<.01$; and mean nurturance: $b=-2.14$, $SE=0.79$, $\beta=-.09$, $P<.01$); the difference between the year 0 and year 3 regression coefficients was not statistically significant ($t=1.31$, $P=.19$) and was, therefore, likely to reflect random sampling variation. Maternal nurturance was not associated with the sex of the child ($P>.23$ for all). The cross-sectional correlations between maternal nurturance and the age of the subjects were $r=-0.09$, $r=-0.08$, and $r=-0.09$ ($P<.01$ for all) for year 0, year 3, and mean maternal nurturance, respectively, suggesting that maternal nurturance was relatively independent of the age of the child.

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ANALYSES OF GENE–ENVIRONMENT INTERACTIONS

The effect of the *HTR2A* genotype–nurturance interaction on depressive symptoms was significant in each of the 3 models (year 0: b=4.62, SE=2.03, *P*=.02; year 3: b=5.01, SE=1.77, *P*=.005; and mean nurturance: b=3.70, SE=1.20, *P*=.002). Among subjects carrying the *T/T* or *T/C* genotypes, there was a significant association between high maternal nurturance and lower levels of adulthood depressive symptoms (year 0: b=−5.10, SE=1.90, β=−.12, *P*=.007; year 3: b=−7.09, SE=1.64, β=−.20, *P*<.001; and mean maternal nurturance: b=−4.60, SE=1.08, β=−.20, *P*<.001); the difference between year 0 and year 3 regression coefficients was not statistically significant (t=1.05, *P*=.29), whereas this association was not observed in subjects carrying the *C/C* genotype in any of the models (*P*>.38 for all).

To further illustrate this interaction, we categorized the subjects according to level of maternal nurturance (low group indicates lowest 25% of subjects; and high group, highest 25% of subjects), and examined the levels of depressive symptoms as a function of the allelic variance of the *HTR2A* gene within these 2 groups (**Figure**). Among subjects with high maternal nurturance, the *HTR2A* genotype was associated with depressive symptoms (analysis of covariance, with age and sex as covariates: year 0, *P*=.07; year 3, *P*<.001; and mean maternal nurturance, *P*<.001), while this was not true among subjects with low maternal nurturance in any of the models (*P*>.28 for all). In the group with high maternal nurturance, subjects carrying the *T/T* or *T/C* genotype scored significantly lower in depressive symptoms than those carrying the *C/C* genotype (effect magnitudes: year 0, η^2=0.02; year 3, η^2=0.08; and mean maternal nurturance, η^2=0.08).

Table 1. Descriptive Statistics for the 1592 Subjects

Variable	Value*
Sex†	
Male	766 (48.1)
Female	826 (51.9)
Age, y	
At year 0	10.9 (5.0)
At year 21	31.8 (5.0)
HTR2A genotype†‡	
T/T	156 (9.8)
T/C	711 (44.7)
C/C	725 (45.5)
Maternal nurturance (transformed)	
Year 0	2.1 (0.3)
Year 3	2.1 (0.4)
Depressive symptoms	
Year 17	44.1 (13.7)
Year 21	42.5 (13.8)

*Data are given as mean (SD) unless otherwise indicated.
†Data are given as number (percentage) of subjects.
‡*HTR2A* is the serotonin receptor 2A gene.

Table 2. Depressive Symptoms by *HTR2A* Genotype*

Depressive Symptoms	Genotype			*P* Value
	T/T	*T/C*	*C/C*	
Year 17 (n = 1112)	42.98 (13.55)	43.96 (13.89)	44.53 (13.50)	.61
Year 21 (n = 1250)	40.98 (14.59)	42.83 (13.92)	42.63 (13.47)	.42
Mean (n = 973)	41.33 (12.54)	43.46 (12.60)	43.72 (12.33)	.26

**HTR2A* is the serotonin receptor 2A gene.

COMMENT

The present results suggest that the *HTR2A* gene may be involved in the development of depression by moderating the influence of childhood and adolescent maternal nurturance on adulthood depressive symptoms. We found that individuals carrying a *T* allele of the *HTR2A* gene were responsive to the protective aspects of nurturing mothering so that in the presence of high maternal nurturance they expressed low depressive symptoms, while this was not true for those carrying the *C/C* genotype. Thus, the levels of depressive symptoms varied as a function of the *HTR2A* polymorphism among individuals with nurturing mothering but not among those exposed to nonnurturing mothering.

Previous molecular gene–environment interaction studies[6-9] have found genetic influences to be accentu-

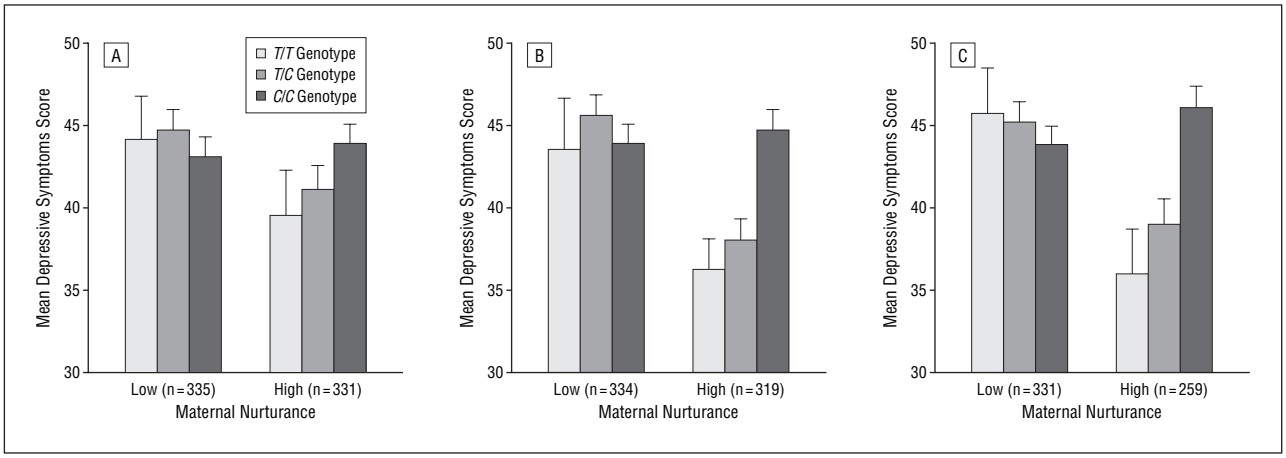

Figure. Depressive symptoms by the serotonin receptor 2A (*HTR2A*) genotype and maternal nurturance group: year 0 nurturance (A), year 3 nurturance (B), and mean nurturance (C). Among subjects with high maternal nurturance, the *HTR2A* genotype was associated with depressive symptoms, while this was not true among subjects with low maternal nurturance (for more information, see the "Analyses of Gene–Environment Interactions" subsection of the "Results" section of the text).

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ated at the detrimental end of the environmental continuum (eg, childhood maltreatment). Herein, the genetic influences were most pronounced among individuals raised in the most beneficial environmental circumstances. Quantitative genetic studies in domains other than depression indicate that genetic variance in some psychologically adaptive characteristics may be accentuated in more favorable environmental conditions.[22] For instance, the heritability of cognitive abilities has been shown to be higher among children of families with high socioeconomic status than among those of families with low socioeconomic status.[23] Following this line of reasoning, we suggest that the *HTR2A* gene is associated with individual differences in responsivity to environmental influences and that in this context it may function as an "opportunity gene" rather than a risk gene (ie, the allelic variance of the *HTR2A* gene may be associated with an ability to use positive aspects of the environment—in the present case, supportive mothering—rather than with heightened vulnerability to negative aspects of the environment).

Until we have replications, we need to be cautious about the present finding. Further research is also needed to understand the moderating role of the *HTR2A* gene. On the neuropsychological level, a path via the prefrontal cortex could be hypothesized.[24] The serotonin 2A receptors are involved in the functioning of the prefrontal cortex,[11,24] and their binding potential has been associated with depression.[10] The prefrontal cortex is involved in cognitive control[25] and regulation of negative emotions,[26] among other functions, and its dysfunctions have been implicated in depression.[27] In addition, the *C* allele of the *HTR2A* gene and dysfunctions of the prefrontal cortex also have been associated with schizophrenia.[28,29]

It would be of interest to study the *HTR2A*–mothering interaction with diagnosed clinical depression as the outcome that, unfortunately, has not been assessed in the Cardiovascular Risk in Young Finns study. Future research should also examine whether the *HTR2A* gene is involved with a specific developmental pathway leading to increased risk of depression. Depression may be associated with emotional dysregulation and externalizing behavioral problems, including attention-deficit/hyperactivity disorder and oppositional defiant disorder, manifest early in life.[30,31] On the other hand, adulthood depression may be preceded by anxious childhood temperament and internalizing behavior.[32,33] Other developmental pathways to adulthood depression are also possible.[34,35]

The fact that the moderating role of the *HTR2A* gene was observed in 2 measurements supports the robustness of the results. We have interpreted our finding as a gene–environment interaction. Given that parental behavior itself is partly heritable,[36] it is possible that the *HTR2A*–mothering interaction reported herein might reflect a gene–gene interaction as well. Future studies should evaluate gene–environment interactions involving the *HTR2A* gene with a variety of different environmental exposures and gene–gene interactions with other genes to assess these 2 possibilities.

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Correspondence: Liisa Keltikangas-Järvinen, PhD, Department of Psychology, University of Helsinki, PO Box 9, FIN-00014, Finland (liisa.keltikangas-jarvinen@helsinki.fi).
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Correction

Errors in Table and Figure. In the Original Article titled "Startle Gating Deficits in a Large Cohort of Patients With Schizophrenia: Relationship to Medications, Symptoms, Neurocognition, and Level of Function," published in the December 2006 issue of the ARCHIVES (2006;63:1325-1335), there are errors in Table 2 and Figure 2A. In Table 2, the third entry under the column heading "Characteristic" should have read, "Psychiatric hospitalizations, mean (range), No." In Figure 2A, the lengths of the error bars have been corrected. The corrected **Figure 2** and its legend are printed here in their entirety.

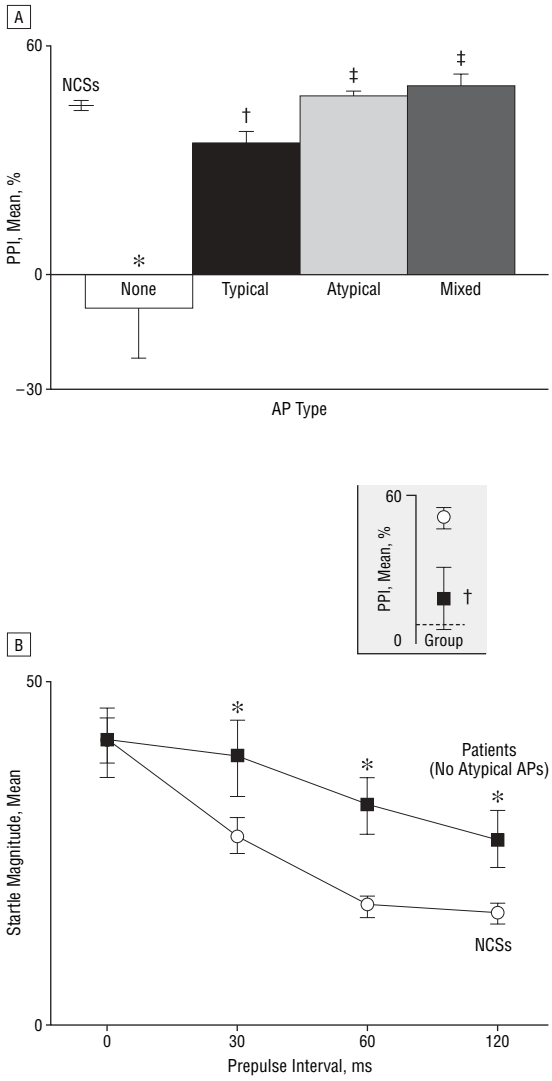

Figure 2. Medication effects on prepulse inhibition (PPI) in patients. A, Mean PPI percentage collapsed across prepulse intervals in patients treated with no antipsychotic medication (AP), typical APs, atypical APs, or both typical and atypical APs. Mean PPI percentage for normal comparison subjects (NCSs) are shown as a single point. Analysis of variance of PPI percentage in patients revealed a significant main effect of medication subgroups ($F_{3,95}$=7.52, P<.001), which was also significant when limited to 60-millisecond prepulse intervals ($F_{3,99}$=6.06, P<.001). Compared with PPI among NCSs, PPI was significantly reduced among unmedicated patients (*P<.001 by Fisher protected least-significant difference) and among all patients not receiving an atypical AP (P=.001); these effects were independent of prepulse interval (all P<.01 for 30-, 60-, and 120-millisecond intervals). Error bars indicate SEM. †P<.005 vs no AP. ‡P<.001 vs no AP. B, Mean startle magnitude on pulse-alone and combined prepulse and pulse trials in patients not receiving atypical APs and case-matched NCSs; groups were balanced precisely for startle magnitude on pulse-alone trials by omitting 1 subject whose startle magnitude on pulse-alone trials was 4.3 SDs above the group mean. Error bars indicate SEM. Analysis of variance of PPI percentage across these groups revealed a significant main effect of diagnosis ($F_{1,34}$=7.39, P<.02) († in inset) and no sex × diagnosis interaction ($F_{1,34}$=3.05, P>.05). Analysis of variance of startle magnitude revealed a significant main effect of trial types ($F_{3,99}$=35.77, P<.001) and a significant interaction of diagnosis × trial type ($F_{3,99}$=5.21, P<.003). Analysis of variance limited to prepulse trials revealed significantly greater startle magnitude on prepulse trials in patients than in NCSs ($F_{1,40}$=15.60, P<.001), reflecting a loss of sensorimotor inhibition. *Significantly greater startle on prepulse + pulse trials in patients than in NCSs after significant interaction of diagnosis × trial type by Fisher protected least-significant difference.

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