On the environmental genetics of depressive symptoms: Focus on two serotonergic genes

Markus Jokela
On the environmental genetics of depressive symptoms: Focus on two serotonergic genes

Markus Jokela

Department of Psychology
University of Helsinki, Finland

Academic dissertation to be publicly discussed,
by due permission of the Faculty of Behavioural Sciences
at the University of Helsinki in Auditorium 6, Metsätalo, Unioninkatu 40,
Helsinki, on the 26th of October, 2007, at 12 o'clock

UNIVERSITY OF HELSINKI
Department of Psychology
Studies 45: 2007
Supervisors:

Professor Liisa Keltikangas-Järvinen
Department of Psychology, University of Helsinki, Finland

Professor Mika Kivimäki
Department of Epidemiology and Public Health, University College London, UK

Reviewers:

Professor Matti Virkkunen
Department of Psychiatry, University of Helsinki, Finland

Professor Jaanus Harro
Department of Psychology, Centre of Behavioural and Health Sciences, University of Tartu, Estonia

Opponent:

Professor Klaus-Peter Lesch
Department of Psychiatry, University of Würzburg, Germany
A devil, born devil, on whose nature
Nurture can never stick; on whom my pains,
Humanely taken, all, all lost, quite lost!
And as with age his body uglier grows,
So his mind cankers. I will plague them all,
Even to roaring.

- Prospero discussing the nature of the devil, From The Tempest
  (William Shakespeare, IV, I, 188-193)

'What will happen to the child if it doesn’t get a Satanic upbringing, though?’ said Aziraphale.

'Probably nothing. It’ll never know.’

'But genetics—'

'Don’t tell me from genetics. What they got to do with it?’ said Crowley. ‘Look at Satan. Created as an angel, grows up to be the Great Adversary. Hey, if you’re going to go on genetics, you might as well say the kid will grow up to be an angel. After all, his father was really big in Heaven in the old days. Saying he’ll grow up to be a demon just because his dad became one is like saying a mouse with its tail cut off will give birth to tail-less mice. No. Upbringing is everything. Take it from me.’

- An angel and a demon discussing the nurture of the devil, From Good Omens
  (Terry Pratchett and Neil Gaiman ©1990, Corgi Books)
Abstract

Depression is a complex psychiatric disorder influenced by several genes, environmental factors, and their interplay. Serotonin receptor 2A (HTR2A) and tryptophan hydroxylase 1 (TPH1) genes have been implicated in vulnerability to depression and other psychiatric disorders, but the results have been inconsistent. The present study examined whether these two genes moderated the influence of different depressogenic environmental factors on subthreshold depressive symptoms (assessed on a modified version of Beck’s Depression Inventory, BDI) and depression-related temperament, i.e., harm avoidance (assessed on the Temperament and Character Inventory, TCI). The environmental factors included measures of childhood and adolescence exposure, i.e., maternal nurturance and parental socioeconomic status, and adulthood social circumstances, i.e., perceived social support and urban/rural residence.

The participants were two randomly selected subsamples (n = 1246, n = 341) from the longitudinal population-based Cardiovascular Risk in Young Finns study (n = 3596). Childhood environmental factors were assessed when the participants were 3 to 18 years of age, and three years after the baseline. Adulthood environmental factors and outcome measures were assessed 17 and 21 years later when the participants were 21 to 39 years of age.

The T102C polymorphism of the HTR2A gene moderated the association between childhood maternal nurturance and adulthood depressive symptoms, such that exposure to high maternal nurturance predicted low depressive symptoms among individuals carrying the T/T or T/C genotypes, but not among those carrying the C/C genotype. Likewise, high parental SES predicted low adulthood harm avoidance in individuals carrying the T/T or T/C genotype, but not in C/C-genotype carriers. Individuals carrying the T/T or T/C genotype were also sensitive to urban/rural residence, such that they had lower depressive symptoms in urban than in rural areas, whereas those carrying the C/C genotype were not sensitive to urban/rural residence difference. HTR2A did not moderate the influence of social support.

The A779C/A218C haplotype of the TPH1 gene was not involved in the association between childhood environment and adulthood outcomes. However, individuals carrying A alleles of the TPH1 haplotype were more vulnerable to the lack of adulthood social support in terms of high depressive symptoms than their counterparts carrying no A alleles. Furthermore, individuals living in remote rural areas and carrying the A/A haplotype had higher depressive symptoms than those carrying other genotypes of the TPH1.

The findings suggest that the HTR2A and TPH1 genes may be involved in the development of depression by influencing individual’s sensitivity to depressogenic environmental influences.

Keywords: Behavior genetics, depression, temperament, harm avoidance, gene–environment interaction, HTR2A, TPH1, childhood

Tutkimukseen osallistujina oli kaksi satunnaisesti valittua ryhmää (n=1246 ja n=343) epidemiologisesta Lasten Sepelvaltimotaudin Riskitekijät (LASERI) -seurantatutkimuksesta (n=3596). Lapsuuden ympäristötekijät arvioitiin osallistujien ollessa 3-18-vuotiaita sekä kolme vuotta tämän jälkeen. Aikuisiän ympäristötekijät sekä masentuneisuus ja temperamentti arvioitiin 17 ja 21 vuotta myöhemmin, kun osallistujat olivat 21-39-vuotiaita.


Tutkimustulosten perusteella HTR2A- ja TPH1-geenin voinevat vaikuttaa masentuneisuuden ja temperamentin kehitykseen muokkaamaalla ihmisten herkkyyttä lapsuuden ja aikuisuuden ympäristötekijöitä kohtaan.

Avainsanat: Käyttäytymisgenetiikka, temperamentti, masennus, geeniympäristö vuorovaikutus, HTR2A, TPH1, lapsu
List of original publications


CONTENTS

1. INTRODUCTION .............................................................................................................8
  1.1. Vulnerability to depression .........................................................................................8
    1.1.1. Subthreshold depressive symptoms .................................................................9
    1.1.2. Temperament .....................................................................................................10
  1.2. Molecular genetics of depression .............................................................................12
    1.2.1. Serotonin receptor 2A (HTR2A) .......................................................................13
    1.2.2. Tryptophan hydroxylase 1 (TPH1) ....................................................................15
  1.3. Environmental influences .........................................................................................17
    1.3.1. Parental behavior ...............................................................................................17
    1.3.2. Childhood socioeconomic status .......................................................................19
    1.3.3. Social support ....................................................................................................20
    1.3.4. Urban/rural residence ........................................................................................21
  1.4. Gene–environment interactions ................................................................................22
  1.5. Aims of the present study .........................................................................................26

2. METHODS AND MATERIALS ....................................................................................28
  2.1. Participants ...............................................................................................................28
  2.2. Study design .............................................................................................................29
  2.3. Measures ...................................................................................................................29
    2.3.1. Dependent variables ..........................................................................................29
    2.3.2. Genotyping ........................................................................................................30
    2.3.3. Environmental measures ....................................................................................30
    2.3.4. Covariates ..........................................................................................................32
  2.4. Statistical analysis .....................................................................................................32

3. RESULTS ........................................................................................................................34
  3.1. Genetic main effects .................................................................................................34
  3.2. Environmental main effects ......................................................................................35
  3.3. Gene–environment interaction effects ......................................................................37
    3.3.1. HTR2A ..............................................................................................................37
    3.3.2. TPH1 ..................................................................................................................41

4. DISCUSSION ..................................................................................................................44
  4.1. Serotonin receptor 2A ...............................................................................................45
  4.2. Tryptophan hydroxylase 1 .......................................................................................47
  4.3. Gene–gene interactions and gene–environment correlations ...................................49
  4.4. Developmental pathways ..........................................................................................50
  4.5. Methodological considerations .................................................................................51
  4.6. An evolutionary afterthought ....................................................................................52
  4.7. Conclusions ..............................................................................................................53

ACKNOWLEDGMENTS ...................................................................................................55
REFERENCES ....................................................................................................................56
ORIGINAL PUBLICATIONS ............................................................................................58
1. INTRODUCTION

Depression is one of the most prevalent psychiatric disorders (Costello et al. 2002, Murray & Lopez 1997). The Health 2000 Study in Finland found that 6.5 percent of Finnish adults had experienced clinical depression during the past year (Pirkola et al. 2005). A recent European multisite study estimated the lifetime prevalence of depression to be approximately 7 to 11 percent (Ayuso-Mateos et al. 2001). In the American National Comorbidity Study (Blazer et al. 1994) from the 1990’s, the lifetime prevalence of major depression was 16 percent. In adulthood, women are two to three times more likely to become depressed than men (e.g. Kornstein 1997, Silverstein 1999).

Depression is a source of considerable disability and morbidity. According to the estimates of the World Health Organization, major depression is the second-ranked cause of disability in industrialized countries (Murray & Lopez 1997). It is estimated that depression will account for 15% of the total disease burden throughout the world by the year 2020 (Murray & Lopez 1997). Depression has negative impacts on social relationships (Joiner 2002) and increases the risk of medical illnesses (Roose 2003, Stover et al. 2003) and suicidal behavior (Arango et al. 2002, Oquendo et al. 1997). Clearly, depression is a major public health concern.

1.1. Vulnerability to depression

The etiology of depression is complex, and many genetic and environmental factors influence the likelihood of its onset. The role of genetic factors in predisposition to depression is well established (Levinson 2006). A recent meta-analysis (Sullivan et al. 2000) of 5 large genetic epidemiological twin studies estimated the heritability of major depression to be 37% (95% confidence interval = 31% – 42%). This estimate did not differ between genders (Sullivan et al. 2000). The moderate heritability indicates that, although genetic influences are involved in the development of depression, a substantial portion of the variance is attributable to environmental factors.
Understanding premorbid vulnerability to clinical depression is considered to be one of the most important aspects of contemporary depression research (Ingram & Siegle 2002). One approach to its study is to focus on individual traits and characteristics that are related to depression but have not yet reached the clinical stage. In this context two measures of individual differences are particularly relevant: subthreshold depressive symptoms and negative affectivity expressed in temperament.

### 1.1.1. Subthreshold depressive symptoms

According to the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV; American Psychiatric Association 1994), the diagnosis of major depression requires the presence of at least four depressive symptoms accompanied by depressed mood or markedly diminished interest or pleasure in daily activities for a minimum of two weeks. The symptoms of depression may include significant weight loss or gain, appetite disturbance, insomnia or hypersomnia, psychomotor agitation or retardation, fatigue or loss of energy, feelings of worthlessness, inappropriate guilt, impaired concentration, recurrent suicidal ideas, or attempted suicide.

A person may exhibit symptoms of depression and Psychological distress without meeting the clinical criteria of diagnosable depression. These symptoms are referred to as “subthreshold” or “subclinical” depressive symptoms (Flett et al. 1997, L. L. Judd et al. 2002, Lewinsohn et al. 2000). Subclinical depressive symptoms in the general population are approximately twice as common as clinical depression (see L. L. Judd et al. 2002). For example, in the Epidemiological Catchment Area study carried out in the United States, the 1-month prevalence of major depressive disorder was 2.3%, while the corresponding percentage was 3.9% for subthreshold symptoms (Judd et al. 1997).

The study of subthreshold depressive symptoms is important for two reasons. First, depressive symptoms are associated with psychological impairment and harmful dysfunctions of behavior, such as performance difficulties in everyday life (Lewinsohn et al. 2000, L. L. Judd et al. 1994, 2002). For example, Judd et al. (1994) found that depressive symptoms correlated with higher levels of household strain, financial strain, and limitations in physical and job function. The second reason to conduct research on
Depressive symptomatology is that it furthers our understanding of the development and etiology of premorbid depression in the general population. While the continuity between subclinical symptoms and clinical depression is still under debate (e.g. Beach & Amir 2003, Coyne 1994, L. L. Judd et al. 2002, Santor & Coyne 2001, Solomon et al. 2001), the evidence indicates that premorbid subclinical depressive symptoms represent a risk for later onset of depressive disorder. In an epidemiological study of over 2000 individuals, Howarth et al. (1992) found the presence of two or more lifetime subthreshold depressive symptoms to predict a 4-fold greater risk of developing a major depressive episode within the next year. Other studies have provided similar findings (Kendler et al. 1993). In sum, the study of subclinical depressive symptoms is important because subclinical symptoms are relevant to people’s well-being and because the study of depressive symptoms may elucidate the etiology of more severe forms of depression.

1.1.2. Temperament
Temperament refers to relatively stable individual differences in early appearing personality traits that are postulated to have specific neurobiological and genetic basis. The dimensions of temperament are related primarily to emotional reactivity and behavioral self-regulation (Cloninger et al. 1987; see Allport 1937, Buss & Plomin 1987, Goldsmith et al. 1987). Individual differences in these dispositions are observed in infants early on: some babies are fussy, easily distressed and difficult to soothe, while others are calm and stoic; some smile and laugh a lot, others show little expression. A number of studies have demonstrated moderate heritability of temperament traits (e.g., Gillespie et al. 2003, Stallings et al. 1996; see Bouchard & McGue 2003).

Reflecting perhaps the biological turn in psychiatry, a recent line of research has sought to relate the development of psychopathology to core dimensions of temperament (Clark 2005, Whittle et al. 2006). One dimension of temperament has emerged as particularly important in this context. This dimension, which is variably labeled as neuroticism, negative affectivity or negative emotionality, is associated with sensitivity to negative stimuli and emotional instability. In the temperament model of Cloninger and colleagues (1987, 1993) this dimension is assessed by harm avoidance, which reflects individual
differences in reactivity to aversive stimuli (Cloninger et al. 1987) and stress vulnerability (Puttonen et al. 2005).

Several studies have shown that depressed patients have higher scores in measures of negative emotionality than non-depressed controls (e.g. Ampollini et al. 1999, Hansenne et al. 1999), and negative emotionality has also been shown to correlate with measures of subthreshold depressive symptoms in non-patient samples (Elovainio et al. 2004, Grucza et al. 2003). Prospective longitudinal studies indicate that negative temperament is a predisposing risk factor of later development of depression (e.g., Kendler et al. 2006; see Klein et al. 2002). This risk appears to be present from early life onwards: A cohort study in New Zealand found that inhibited behavior at age three predicted increased risk for the development of depression in young adulthood (Caspi et al. 1996, Jaffee et al. 2002; see Gladstone & Parker 2006).

Quantitative genetic studies suggest that negative temperament may not only predispose to depression, but that the two may share a common genetic basis. Results from several twin studies indicate that approximately 55% to 70% of the genetic vulnerability to depression is shared with the genetic basis of negative emotionality (Fanous et al. 2002, Kendler et al. 1993, Kendler et al. 2006; see also Hettema et al. 2004). Similarly, a family study of clinical depression suggests that harm avoidance temperament may represent genetic vulnerability to the development of depression (Farmer et al. 2003).

The genetic correlation between negative emotionality and depression indicates that temperament may be considered as an endophenotype for depression. The term “endophenotype” refers to intermediate phenotypes between genes and complex phenotypes of interest which can be neurobiological, neuropsychological or cognitive in nature (Gottesman & Gould 2003). Endophenotypes are of interest to psychiatric genetics because they allow us to trace the pathways from genes to complex phenotypes of interest (Hasler et al. 2004). In the case of depression, subthreshold depressive symptoms and temperament may be considered as measures of genetic vulnerability to clinical depression.
1.2. Molecular genetics of depression

Although quantitative genetic studies have demonstrated that temperament and depression exhibit moderate heritability (Sullivan et al. 2000), they do not tell what specific genes are involved. The first studies to explore the molecular basis of human behavior were carried out over forty years ago by Cohen and Thomas (1962), who compared the distribution of blood groups in smokers and nonsmokers. In a related vein, Cattell et al. (1964) searched for associations between blood groups and personality traits. Perhaps not unexpectedly, the success of these early explorations was meager.

The first modern studies of associations between genes and human behavior were published in 1996. One of the studies reported an association between the serotonin transporter gene 5-HTTLPR and anxiety-related personality (Lesch et al. 1996), and two others an association between the dopamine receptor gene DRD4 and novelty seeking (Benjamin et al. 1996, Ebstein et al. 1996). These papers were quickly followed by an increasing number of studies reporting or failing to report associations between different genes and a variety of psychological phenotypes (e.g. Flory et al. 1999, Jönsson et al. 1998, Keltikangas-Järvinen et al. 2003, Mazzanti et al. 1998, Vandenbergh et al. 1997; for reviews see Gestel & Broeckhoven 2003, Ebstein 2006, Munafò et al. 2003, Reif & Lesch 2003; see section 1.4. below).

Most of the molecular genetic studies of depression have concentrated on serotonergic genes because serotonin has been implicated in the development of depression by several lines of research (Booij & Van der Does 2007, Jans et al. 2007). For instance, depression has been related to lower levels of concentrations of CSF 5-HIAA and to dysfunctions of serotonin transporter and receptors (Nemeroff et al. 1994, Oquendo & Mann et al. 2001). Serotonin is also postulated to be the primary neurotransmitter underlying the temperament trait harm avoidance with support coming from empirical evidence (e.g. Gerra et al. 2000, Hansenne and Ansseau 1999; see Cloninger 2000).

Given the role of serotonin in depression and temperament, we selected two serotonergic candidate genes – the serotonin receptor 2A (HTR2A) and tryptophan hydroxylase 1 (TPH1) – for the present studies investigating the development of depressive symptoms and harm avoidance.
1.2.1. Serotonin receptor 2A (HTR2A)

At present there is evidence for the existence of at least 16 different subtypes of serotonin receptors. The 5-HT$_2$ receptor family is comprised of three subtypes: 5-HT$_{2A}$, 5-HT$_{2B}$ and 5-HT$_{2C}$. The 5-HT$_{2A}$ receptors occur both peripherally and centrally. In the brain the receptors are located predominantly in the prefrontal cortex, claustrum, olfactory nuclei and basal ganglia, where they modulate the activity of other neurotransmitters (e.g. glutamate, dopamine, acetylcholine and noradrenaline), and the 5-HT$_{2A}$ receptors have been shown to modulate the activation of dopaminergic neurons in the prefrontal cortex (Botrolozzi et al. 2005, DiMatteo & Esposito 2003).

Brain imaging studies suggest that the binding potential of the 5-HT$_{2A}$ receptors in the brain is decreased in depressed individuals (Oquendo & Mann 2001; see also Yatham et al. 2000, Sheline et al. 2004), though Meyer et al. (2003) reported an association between high rather than low prefrontal 5-HT$_{2A}$ binding potential and depression. The lower binding potential of 5-HT$_{2A}$ receptors has also been associated with higher harm avoidance (Moresco et al. 2002, van Heeringen 2003) and higher hopelessness (van Heeringen 2003), suggesting a role of 5-HT$_{2A}$ receptors in the development of anxious temperament. In line with this, two studies (Nelson et al. 1996, Peirson et al. 1999) have demonstrated a negative correlation between blood platelet 5-HT$_{2A}$ receptors and harm avoidance.

Located in the long arm of chromosome 13, the serotonin receptor 2A gene (HTR2A) contains at least three common variable polymorphisms. Of these, the T102C polymorphism has been the most intensively investigated. It is located in exon 1 near the gene’s promoter region, suggesting that it might have some role in gene regulation. The T102C is in complete linkage disequilibrium (LD) with another polymorphic site of the gene referred to as -A1348G, which, in turn, has been shown to be in LD with a third polymorphism, -783A/G (Myers et al. 2007).

The C allele of the T102C polymorphism of the HTR2A gene has been associated with low binding potential of the 5-HT$_{2A}$ receptors (Turecki et al. 1999), and with low levels of 5-HT$_{2A}$ receptor mRNA in postmortem brain (Polesskaya & Sokolov, 2002), although a recent study (Bray et al. 2004) found no evidence of a polymorphism in the HTR2A gene.
affecting the levels of mRNA in the adult brain. Furthermore, the T102C has been found to be in complete LD with the -1438A/G polymorphism of the HTR2A gene (e.g. Bray et al. 2004, Spurlock et al. 1998). In a recent study, Myers et al. (2007) reported that variation in gene expression was associated with the -1438A/G polymorphism of the HTR2A and that this association was further moderated by the -783A/G polymorphism.

Studies of a genetic association between HTR2A and depression have provided mostly inconsistent results (for a review, see Norton & Owen 2005). One study has reported an association between the C allele and increased depression risk (Du et al. 2000), while two studies have linked the T rather than the C allele with increased risk of depression (Eley et al. 2004, Zhang et al. 1997). Most studies have failed to replicate either of these associations (Frisch et al. 1999; see Anguelova et al. 2003), and there appears to be no association between the HTR2A and bipolar disorder either (Blairy et al. 2000, Vincent et al. 1999). Arias, Gutierrez et al. (2001) reported that carriers of the C allele were more likely to show a seasonal pattern in depression than carriers of the T allele, and that C-allele carriers may also have a poorer response to antidepressant treatment (Peters et al. 2004).

The HTR2A has also been associated with suicidal behavior, in that individuals carrying the C allele have been found to exhibit more suicidal ideation (Du et al. 2000) and to be more likely to commit suicide than individuals carrying the T allele (Arias, Gasto et al. 2001). However, a recent meta-analysis (Li et al. 2007) based on 25 studies concluded that the T102C polymorphism of the HTR2A gene is not robustly associated with suicidal behavior.

Studies examining the relation between HTR2A and temperament or personality have also provided inconsistent results. In a sample of patients with schizophrenia or affective disorders, Golimbet et al. (2002) found that individuals carrying the C/C genotype of the HTR2A gene had higher neuroticism than individuals carrying the T/T or T/C genotypes. In a relatively small sample of bipolar subjects, Blairy et al (2000) found no association between HTR2A and harm avoidance (HA) as measured by Cloninger’s TPQ questionnaire. Furthermore, three other studies have found no evidence of an association between HTR2A and HA (Kusumi et al. 2002, Jönsson et al. 2001, Schüssler et al. 2000).
1.2.2. Tryptophan hydroxylase 1 (TPH1)

Serotonin is synthesized from the amino acid tryptophan, which is transported from blood to the brain. As tryptophan hydroxylase (TPH) is the rate-limiting enzyme in the biosynthesis of serotonin, it is a crucial step in serotonin functioning (Young and Leyton 2002). It determines the amount of serotonin available in the brain: increasing (decreasing) the levels of tryptophan increases (decreases) the levels of serotonin. In an experimental paradigm of acute tryptophan depletion (ATD) the tryptophan levels of subjects are lowered by administration of a special diet. Experimentally induced tryptophan depletion has been found to lead to negative mood (see Young & Leyton 2002, Van der Does 2001), providing evidence for the hypothesis that TPH may be related to affective disorders. Moskowitz et al. (2000), in turn, found that a two-week treatment of tryptophan increased dominant behavior and decreased quarrelsome behavior in healthy volunteers.

Due to their central role in serotonin synthesis, genes encoding for TPH are regarded as candidate genes regarding susceptibility to psychiatric disorders, including depression. Two TPH genes, TPH1 and TPH2, located in the short arm of chromosome 11 and the long arm of chromosome 12, respectively, have been identified in humans. Studies on rodents (Patel et al. 2004, Walther et al. 2003, Zhang et al. 2004) suggest that TPH1 is primarily expressed peripherally (e.g. in the duodenum) and only in small amounts in the brain (e.g. in the pineal gland). However, a human postmortem study (Zill et al. 2007) found that TPH1 was expressed in several areas of the brain, e.g., in the hypothalamus and amygdala. Furthermore, Nakamura et al. (2006) found in rodents that TPH1 was associated with brain serotonin levels during late development, but not in adults, suggesting that TPH1 may be involved in the development of serotonergic neurons (Nakamura et al. 2006).

Most of the molecular genetic studies of TPH1 to date have examined one of the two polymorphisms of TPH1 – A218C and A779C – which have been found to be in complete or strong LD in previous studies (Nielsen et al. 1997). They are located in an intron of TPH1 and are assumed to be in LD with some other functional polymorphism nearby (Nielsen et al. 1997, Rotondo et al. 1999). Rotondo et al. (1999) demonstrated an LD between the A779C polymorphism and a polymorphism in the promoter region of the gene. Furthermore, a strong LD between the A218C polymorphism and a possible functional
polymorphism in the promoter region was recently reported by Sun et al. (2005), suggesting that the intronic A218C and A779C polymorphisms may serve as markers for this promoter polymorphism.

The first studies associating TPH1 gene with psychiatric disorders were carried out in Finnish impulsive offenders, among whom TPH1 was found to be associated with suicidality and alcoholism (Nielsen et al. 1994, 1998). Since the preliminary studies of Nielsen et al. (1994, 1998), the majority of TPH1 association studies have focused on suicidal behavior. Three meta-analyses have been conducted to assess the reliability of the association between TPH1 and suicidal behavior. The first of them found no overall association of TPH1 with suicidal behavior (Lalovic & Turecki 2002), whereas the other two (Rujescu et al. 2003, Bellivier et al. 2004) concluded that the A-allele of TPH1 polymorphism has a small yet significant effect on the risk of suicidal behavior (see also Bondy et al. 2006). The difference between the first and the two subsequent meta-analyses appears to be due to inclusion of different studies.

The A allele of the TPH1 has also been associated with an increased susceptibility to bipolar disorder (Bellivier et al. 1998, Lai et al. 2002), but a number of subsequent studies have failed to find this association in either bipolar (Furlong et al. 1998, Kirov et al. 1999, Lai et al. 2005, McQuillin et al. 1999) or major depressive disorders (Frisch et al. 1999, Furlong et al. 1998, Serretti, Lilli et al. 2001). Du et al. (2001) found the A allele to be associated with increased somatic anxiety among depressive patients, and one study found the A allele to be associated with elevated deliberate self-harm (Pooley et al. 2003). On the neurobiological level, the A allele has been associated with lower CSF 5-HIAA levels in healthy volunteers, although only in men (Jönsson et al. 1997), suggesting lower serotonergic functioning in individuals carrying the A allele. Nielsen et al. (1994) also found an association between TPH1 and 5-HIAA in a sample of patients, but it was in the opposite direction than in the study of Jönsson et al. (1997), which may reflect differences between the samples (i.e., healthy volunteers vs. impulsive/aggressive patients). Furthermore, there is evidence suggesting that the A allele may be associated with a poorer response to the psychopharmacological treatment of depression (Peters et al. 2004; Serretti, Zanardi et al. 2001).
1.3. Environmental influences

Several environmental factors have been shown to affect the risk of depression (e.g. Kendler et al. 2002, 2006; Kessler et al. 1997), and research suggests that childhood and adulthood social environments are both relevant in understanding the etiology of depression. Adverse childhood experiences have been found to predispose to later depressive disorders (e.g. Gilman et al. 2002, Kessler et al. 1997, Repetti et al. 2002), suggesting that childhood may be a critical period for the development of long-term psychological vulnerability (see Leonardo & Hen 2006). A latent vulnerability may then progress into a clinical disorder in response to stressful adulthood environments, as postulated by stress-diathesis models of psychiatric disorders (Costello et al. 2002, Monroe & Simons 1991).

In the present study we were interested in two factors related to childhood environment, i.e., maternal nurturance and parental socioeconomic status, and two factors related to adulthood social circumstances, i.e., social support and urban/rural residence. Previous research has suggested that these may be relevant environmental factors for depressive symptoms and temperament, and this research literature is reviewed next. However, it must be noted at the outset that these factors may not represent “pure” environmental factors, but may involve heritable variation – a point which we will return to in section 4.3 (see Plomin & Bergeman 1991).

1.3.1. Parental behavior

The long-term consequences of early childhood experiences with parents have received much attention in developmental psychology (Collins et al. 2000, Goodman 2002, Maccoby 2000, Repetti et al. 2002). Family environment and parental behaviors have been considered important in the development of stress responsivity (e.g. Cameron et al. 2005, Leckman et al. 2004, Taylor et al. 2004) and psychiatric disorders (e.g. Pike et al. 1996). A number of studies have shown that children exposed to severe abuse or maltreatment are more likely to develop depression and anxiety disorders as adults (e.g. Heim et al. 2002; see Heim & Nemeroff 1999). Even more moderate parental behaviors, such as negligence and
high levels of family conflict, or a lack of warmth and emotional support, have also been related to psychological distress (e.g. Johnson et al. 2001, 2006; see Rapee 1997) and physical illness (Pulkki et al. 2003) in children.

Repetti et al. (2002) have coined the term “risky family” to refer to families characterized by conflict, unaffectionate interaction styles and a lack of nurturance. Reviewing a large body of evidence, they show that risky families predispose children to a range of mental and physical illnesses, including depression. They also note that parents with low socioeconomic status (SES) are more likely to use harsh discipline and coercive parenting styles, suggesting that parental behavior might explain part of the association between SES and health in children (Repetti et al. 2002). For example, Lehman et al. (2005) reported that low parental SES was associated with harsh and conflict-ridden family environment which, in turn, predicted increased risk of depression and hostility in adulthood. In the Cardiovascular Risk in Young Finns study, mothers’ life dissatisfaction and type-A behavior predicted increased adulthood hostility in their offspring (Keltikangas-Järvinen & Heinonen 2003).

Experimental studies on non-human animals also indicate that stressful early rearing environments can have long-term negative effects on psychological well-being (see Sánchez et al. 2001, Suomi 1999). In an experimental protocol used to evaluate the impact of early adverse life experiences, rhesus infants, who are normally reared by their mothers, are separated from them and reared in groups of non-adult peers. Monkeys reared only by their peers are deprived of parental supervision and opportunities to learn appropriate social behavior from their mothers. Studies applying this protocol have demonstrated that compared to mother-reared monkeys, peer-reared monkeys show impairments in adulthood social behaviors, and also appear to be more reactive to stress (e.g. Barr et al. 2003, Barr et al. 2004, Newman et al. 2005; see Suomi 1999). Studies on rodents have provided similar findings on the relevance of early life experiences and parental care (see Leckman & Herman 2002, Meaney 2001).
1.3.2. Childhood socioeconomic status

Socioeconomic status (SES) of the parents is a widely studied measure reflecting the quality of early developmental environment. SES is a global construct assessing the availability of social, financial and human capital (Bradley & Corwyn 2002). There is no single agreed-upon way to measure SES, but level of completed education, income, or occupational status, or a combination of these, is generally used as an indicator of SES. SES is one of the most extensively studied environmental factors associated with physical and mental health, and it has been found to predict almost all aspects of health (e.g. Kivimäki et al. 2006, Pulkki et al. 2003; for reviews see Bradley & Corwyn 2002, Brooks-Gunn & Duncan 1997, McLloyd 1998). Regarding depression, adults with low SES have an approximately two times greater risk of depressive disorder than those with high SES (Lorant et al. 2003).

The association between SES and health may have its origins already in childhood. Children from families with low SES are disadvantaged in cognitive and emotional development and they have more mental and physical health problems than children from families with high SES (see Bradley & Corwyn 2002, Brooks-Gunn & Duncan 1997, McLoyd 1998). Longitudinal studies suggest that the influence of parental SES may have long-lasting health consequences extending to adulthood: childhood SES has been found to predict physical health in adulthood independently of adulthood SES (e.g. Marmot et al. 2001, Poulton et al. 2002).

With respect to mental health, low childhood SES has been shown to predispose to the development of adulthood depression. In a 29-year longitudinal study of over 1000 participants, Gilman et al. (2002) found that children with low SES backgrounds had nearly a twofold increased risk for adulthood major depression compared to those with the highest SES background. This association was independent of adulthood SES (Gilman et al. 2002) and of childhood parental divorce and conflict (Gilman et al. 2003). In an inter-generational study Ritsher et al. (2001) demonstrated that parental SES predicted heightened risk of depression independently of depression in parents. Moreover, childhood SES also predicts a poorer prognosis for depressed individuals, in that low childhood SES increased the risk of recurrence of depressive episodes and reduced the likelihood of remission from
depressive episodes (Gilman et al. 2003). This suggests that childhood SES may have a broad influence on depression vulnerability at different stages of the disorder.

It has been suggested that the impact of low childhood SES on psychiatric vulnerability is mediated by impaired socio-emotional development and coping skills, so that children of families with low SES tend to become less resilient to stress than children of families with high SES (see Cameron et al. 2005, Repetti et al. 2002). Children growing up in families with high SES have better access to a variety of resources that may buffer negative experiences and enhance positive opportunities (Bradley & Corwyn 2002). Individuals growing up in low SES circumstances are more likely to be exposed to threatening and uncontrollable life circumstances and environmental hazards than their counterparts with high parental SES, and exposure to chronic social strain is likely to compromise resilience to later stress (Brooks-Gunn & Duncan 1997, McLloyd 1998).

1.3.3. Social support
Although adverse childhood experiences have been associated with increased vulnerability to depression, adulthood social environments also play a role. Extensive research indicates that social support is an important protective factor in maintaining good physical and mental health (Brown and Andrews 1986, Cohen and Willis 1985, House et al. 1988, Katainen et al. 1999). Social support refers to available interpersonal resources for coping with potentially harmful experiences, be they major life events or daily hassles (Thoits 1995). Prospective studies (e.g. House et al. 1982) have demonstrated that mortality from all causes is greater among persons with low levels of social support (see House et al. 1988). The health effects of social support are comparable to standard risk factors such as smoking, blood pressure and physical activity (House et al. 1988).

Numerous studies have demonstrated a relationship between social support and major depression or depressive symptoms (see Cohen & Wills 1985 for a review). Higher support decreases the risk of depressive episode onset (House and Landis 1988), increases the likelihood of remaining healthy when confronted with stressful life events (Sarason et al. 1994) and predicts shorter recovery time from depressive episodes (Johnson et al. 1999). In the Cardiovascular Risk in Young Finns sample, Heponiemi et al. (2006) found that social
support predicted low depressive symptoms independently of childhood/adolescent anger and hostility (see also Katainen et al. 1999). Low social support has also been associated with increased risk of suicidal behavior (de Mann and Leduc 1995, Esposito et al. 2002; see also Durkheim 1963/1897).

Social support may exert its protective influence both directly and indirectly, referred to as the “main effect model” and the “buffering model”, respectively. The former model maintains that social relationships are important and beneficial for mental health in themselves and independently of other life circumstances. The buffering model postulates that social support in itself may not promote better health, but that the benefits of social support emerge when individuals are confronted with stressful life experiences. Both models have received supporting empirical evidence (see Cohen & Wills 1985), suggesting that social support acts both as an independent factor and as a resource that can buffer stress.

1.3.4. Urban/rural residence
Most research on depression has focused on individual-level experiences, but depressogenic influences may also be present in characteristics of the neighborhood and community (Cutrona et al. 2006, Leventhal & Brooks-Gunn 2000). This line of research has not been studied as systematically and thoroughly as the other risk factors discussed above. Most of the studies of neighborhood influence have investigated criminal and antisocial behavior (see Sampson et al. 2002), and have found that poor neighborhoods function as catalysts for these behaviors. Regarding psychiatric disorders, urbanicity has been consistently linked with increased risk for schizophrenia (McGrath & Scott 2006), although the causal mechanisms responsible for this association remain unknown.

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 (Lehtinen et al. 2005, Romans-Clarkson et al. 1990). These inconsistent results suggest that the influence of
socioregional factors is likely to vary by society and population (for reviews see F. K. Judd et al. 2002, Verheij 1996).

The mechanisms mediating the potential depressogenic influence of 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).

Previous studies carried out in Finland (Lehtinen et al. 2005, Lehtinen & Joukamaa, 1994) have found no differences in the prevalence of depression between rural and urban regions, suggesting the 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 the 1960s onwards increasing migration from rural regions to city centers 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, higher rates of morbidity and suicide, higher prevalence of substandard housing, and fewer opportunities for employment (Kainulainen et al. 2001, Karvonen & Rintala 2004). Given that social and economic hardships are known to be associated with poorer mental health (Lorant et al. 2003), rural residency in Finland can be hypothesized to confer an increased risk of the development of depressive symptoms. Indeed, in the Northern Finland birth cohort study (Joukamaa et al. 2003) rural residence was found to be associated with higher alexithymia, i.e., low mood, than was urban residence.

1.4. Gene–environment interactions
The study of molecular genetics of behavior is still in its early stages, and this is reflected in its modest success to date. In general, the results of simple association studies reporting connections between genotypes and psychological traits have been rather inconsistent and
inconclusive (Gestel & Broeckhoven 2003, Hamer 2002). Replication studies have provided mixed evidence for the original findings, and several meta-analyses have found no strong evidence for robust associations between specific genes and psychiatric disorders or personality dimensions (e.g. Li et al. 2006, Munafò et al. 2003). Perhaps most tellingly, even different meta-analyses examining the same and most extensively studied associations have come to conflicting conclusions (e.g. the association between the 5-HTTLPR gene and negative temperament (Sen et al. 2004, Schinka et al. 2004, Munafò et al. 2004). On the other hand, some robust associations have been identified (e.g. Abdolmaleky et al. 2004, Li et al. 2007).

The limited success of simple association studies has led behavior geneticists to seek new avenues of research which would provide more robust and convincing results (Ebstein 2006, Hamer 2002, Reif & Lesch 2003). One of these has been the study of interplay between genes and environment, which is one of the most promising molecular genetic study designs (Caspi & Moffitt 2006, Lesch 2004, Moffitt et al. 2005). Studies with measured genes and environmental variables provide a more reliable research paradigm for gene–environment investigations than earlier methods of quantitative genetics (Moffitt et al. 2005, Rowe 2003; see Wachs & Plomin 1991). The inclusion of relevant measures of environmental exposure into molecular genetic studies should give a more complete picture of the role of specific genotypes in psychological development.

The idea of gene–environment interaction is, of course, not new. Already in 1938, J.B.S. Haldane, an evolutionary biologist, noted that genetic differences might explain the variability in responses of industry potters to unhealthy work conditions. Shanahan & Hofer (2005) have presented a useful description of the interplay between genes and environment. First, the environment may act as a trigger, turning genetic potential into phenotypic actuality. In the absence of such an environmental trigger, genetic liability is not expressed in the phenotype. Second, environmental influences may compensate for a genetic liability. That is, a genetic liability may not be expressed because it is buffered by enriched environmental input. Third, the environment may control and restrict the expression of genetic tendencies. Here genetic differences are most pronouncedly expressed in the absence of environmental contributions. Finally, environmental input may enhance the
beneficial and adaptive effects of a gene. Here one would expect the genetic effects to be most pronounced in those environments richest in resources.

Empirical evidence from quantitative genetic studies illustrates different kinds of gene–environment interactions. Kendler et al. (1995) found that genetic liability to depression was most clearly observed among women who had encountered severe life events (environment as a trigger). Heath and colleagues (1989) showed that the heritability of alcoholism was lower in married women than in single women, suggesting that marriage may attenuate heritable alcoholism (environment as a buffer). In a study of Dutch twins, religious upbringing was found to suppress heritable tendencies in alcohol use (Koopmans et al. 1999) and in disinhibited behavior (environment as a control). Finally, the heritability of cognitive abilities has been shown to be higher among children with high parental SES than in their lower SES counterparts (Harden et al. 2007, Turkheimer et al. 2003), indicating that high parental SES allows genetic dispositions to emerge more freely (environment as an enhancer).

The first molecular genetic demonstrations of gene–environment interactions in human behavior involved the dopamine receptor gene DRD2 and family environment (Berman & Noble 1997, Ozkaragoz & Noble 2000). In a sample of adolescent boys, Berman and Noble (1997) showed that family stress correlated negatively with cognitive functioning in boys carrying the “minor” allele of the DRD2, but not in carriers of “major” alleles. In the same sample, Ozkaragoz and Noble (2000) demonstrated that parental alcoholism was associated with high extraversion among boys carrying a minor allele of the DRD2 but not in those carrying only major alleles. Madrid et al. (2001), in turn, found that experienced economic stress was more strongly associated with alcoholism in individuals carrying the minor allele than in those carrying only major alleles. In the Cardiovascular Risk in Young Finns study, the DRD2 has been shown to moderate the impact of family or job loss on depressive symptoms (Elovainio et al. 2007; see also Keltikangas-Järvinen et al. 2004, Lahti et al. 2005, Elovainio et al. 2004).

One of the most studied gene–environment interactions has involved the serotonin transporter 5-HTTLPR polymorphism and negative life events in the development of depression (Caspi et al. 2003; see Moffitt et al. 2005). Negative life events, such as marital
conflict, job loss, illness and injury, are considered to be key elements in the onset of depression. Caspi et al. (2003) found that the impact of adverse life events on depression was stronger in individuals carrying one or two “short” alleles of the 5-HTTLPR than in those carrying only “long” alleles. This finding has been replicated in a number of studies (Cervilla et al. in press, Eley et al. 2004, Grabe et al. 2005, Kendler et al. 2005, Kim et al. in press, Zalsman et al. 2006; however, see Gillespie et al. 2005, Surtees et al. 2006 for nonreplications). The study of Eley et al. (2004) also examined the TPH1 and HTR2A genes, but found no interaction between these genes and social stress in determining depression in adolescents.

The study of Caspi et al. (2003) also showed that the 5-HTTLPR gene moderated the impact of childhood maltreatment on adulthood depression. Exposure to childhood maltreatment predicted increased risk of depression particularly in individuals carrying the short rather than the long alleles of the 5-HTTLPR. Roy et al. (in press) demonstrated a similar interaction effect between the 5-HTTLPR and childhood trauma on suicide risk. Furthermore, Kaufman et al. (2004) showed that the 5-HTTLPR polymorphism moderated the influence of maltreatment on depression in children, and that this interaction effect was further moderated by the availability of social support. Maltreated children with the s/s genotype and no social support had higher depression scores than maltreated children with the s/s genotype who had adequate social support. These findings provide empirical evidence for the hypothesis (Leonardo & Hen 2006) that gene–environment interactions in early life may have long-term impacts on depression vulnerability later in life.

Studies on nonhuman primates, who have an rh5-HTTLPR gene analogous to that of human 5-HTTLPR, have provided similar results (see Barr et al. 2003). Genotypic differences in the rh5-HTTLPR have been found to be accentuated in peer-reared, and therefore more stressed, monkeys compared to mother-reared monkeys. Among peer-reared monkeys, the short allele has been associated with lower cerebrospinal fluid concentrations of the serotonin metabolite 5-hydroxyindoleacetic acid (Bennett et al. 2002), lower orientation score (Champoux et al. 2002; see also Barr et al. 2003, Newman et al. 2005), and exaggerated endocrinological response to social separation (Barr et al. 2004).
A functional polymorphism in the monoamine oxidase A (MAO-A) gene has also received much attention in gene–environment interaction research. Exposure to childhood maltreatment appears to result in later antisocial and criminal behavior more likely among individuals carrying the low-activity genotype of the MAO-A than among individuals carrying the high-activity MAO-A (Caspi et al. 2002). This finding has been replicated in several studies (e.g. Foley et al. 2004, Haberstick et al. 2005, Nilsson 2006, Widom & Brzustowicz 2006; see Kim-Cohen et al. 2006), suggesting a relatively robust gene–environment interaction.

In sum, a growing research literature is pointing to the usefulness of gene–environment interactions in identifying the role of genetic influences in the development of behavior. Most studies to date have found evidence for interactions where adverse environmental factors (e.g. maltreatment, negative life events) act as triggers that accentuate the genetic risk associated with particular alleles. The genetic differences have therefore been most accentuated among those who have been exposed to deleterious experiences.

1.5. Aims of the present study

Although evidence from neurobiological and brain imaging studies suggest that the HTR2A and TPH1 genes may be relevant in the development of depressive symptoms and harm avoidance, the evidence from genetic association studies has been inconclusive. Recent molecular genetic research indicates that specific genes may affect psychological traits indirectly by moderating environmental factors rather than being directly associated with them. Here we examined if the T102C polymorphism of the HTR2A gene and the A779C and A218 C polymorphisms of the TPH1 gene moderate the influence of depressogenic childhood and adulthood environments on depressive symptoms and harm avoidance.

First, we examined whether the HTR2A and TPH1 moderate the influence of maternal nurturance in childhood and adolescence on depressive symptoms in adulthood. We then examined if a similar gene–environment interaction involving childhood environment can be demonstrated with measures conceptually related but empirically independent from those used in the first study. Hence, we examined the interaction effect between the genes and parental socioeconomic status (related to childhood environment as maternal
nurturance) on temperament trait harm avoidance (related to depressive symptoms). Next, we examined if the HTR2A and TPH1 genes moderate the influence of adulthood social environment, namely perceived social support and urban/rural residence, on depressive symptoms.

We hypothesized that low childhood maternal nurturance and low parental SES are associated with high depressive symptoms and high harm avoidance, respectively, in adulthood. We also expected low adulthood social support and rural residence to predict high depressive symptoms. As the C allele of the T102C polymorphism of the HTR2A gene and the A alleles of the TPH1 A779C and A218C polymorphisms have been identified as the risk alleles for psychiatric disorders, we hypothesized that these alleles are associated with high depressive symptoms and HA, and that individuals carrying these alleles are more vulnerable to depressogenic environmental influences.
2. METHODS AND MATERIALS

2.1. Participants

The participants were women and men participating in the on-going population-based study of Cardiovascular Risk in Young Finns (Åkerblom et al. 1991, Raitakari et al. 2003). In this study, a randomly selected sample of 3596 Finnish healthy children and adolescents from six birth cohorts (aged 3 to 18 years at the baseline) has been followed since 1980. In order to select participants that are broadly representative of Finnish children and adolescents in terms of living conditions and socioeconomic and demographic background, Finland was divided into five areas according to the location of the university cities with a medical school (Helsinki, Kuopio, Oulu, Tampere and Turku). In each area, urban and rural boys and girls were randomly selected on the basis of their personal social security number from the Social Insurance Institution’s population register, which covers the whole population of Finland. In four areas (Helsinki, Tampere, Turku and Oulu), 60 girls and 60 boys in the age cohorts of 3, 6, 9, 12, 15, and 18 years in 1980 were selected. To ensure equal numbers of participants from the east and the west, 120 boys and 120 girls were selected in each cohort in Kuopio, the most eastern area (Åkerblom et al. 1991).

The initially selected sample of the CRYF consisted of 4,320 children and adolescents. The first and second pilot studies were carried out in 1978 and 1979. The first cross-sectional study was performed in 1980, and it included 3,596 children and adolescents (83.2% of the invited). These cohorts have had medical and psychological follow-up examinations up in 1983, 1986, 1989, 1992, and 2001. The participation rates for the follow-up studies were 83%, 78%, 76%, 66%, and 64% of the original study sample (N=3,596) in 1980 (Åkerblom et al. 1999; Viikari 2003). Complete details of the sample are given elsewhere (Åkerblom et al. 1991, Raitakari et al. 2003). The study was approved by local ethics committees, and all subjects gave their written informed consent and gave blood samples in accordance with the Helsinki Declaration.

The participants of the present study were two randomly selected subsamples from the main sample: In studies involving the HTR2A gene the sample included 1246 individuals (687 women, 559 men) and in studies involving the TPH1 gene the sample included 341
individuals (186 women, 155 men). The sample sizes varied somewhat in different analyses depending on variables included in the models.

2.2. Study design

The outcome variables, i.e., depressive symptoms and harm avoidance, were assessed in two test settings 17 and 21 years after the baseline (referred to as Years 17 and 21), when the participants were 20 – 35 and 24 – 39 years of age, respectively. Gene–environment interactions involving childhood and adolescence environment were assessed in a prospective longitudinal study design, where maternal nurturance and parental SES were assessed at baseline and three years later (referred to as Years 0 and 3), when the participants were 3 – 18 and 6 – 21 years of age, respectively. In order to study the influence of social support prospectively, social support was measured in Year 17 and used to predict depressive symptoms in Year 21. The association between urban/rural residence and depressive symptoms was assessed cross-sectionally in Year 21 with two measures of residence, and prospectively with one measure of residence assessed in Year-17.

2.3. Measures

2.3.1. Dependent variables

Depressive symptoms were assessed using a modified version of Beck’s Depression Inventory (BDI; Beck & Steer 1987). In the original version of the BDI, subjects 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 items of the scale were the second mildest statements of the original BDI items (e.g. “I often feel sad”). The subjects were asked to rate each of the 21 items on a five-point scale ranging from totally disagree (1) to totally agree (5). 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 $\alpha > .90$, and the correlation between Year-17 and Year-21 depressive symptoms was $r = .65$ ($p < .001$).
Harm avoidance was assessed with the Temperament and Character Inventory (TCI) developed by Cloninger et al. (1993). The HA scale consists of 35 items which were self-rated by the subjects on a five-point scale ranging from totally disagree (1) to totally agree (5). The Cronbach’s alpha reliabilities were $\alpha > .90$, and the correlation between Year-17 and Year-21 HA was $r = .78$ ($p < .001$).

2.3.2. Genotyping

TPH1 218 A>C and 779 A>C, and HTR2A 102 T>C genotypes were determined by extracting genomic DNA 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 7900HT Sequence Detection System (Applied Biosystems, Foster City, CA, USA). 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 (HTR2A rs6313; TPH1 A218C rs1800532; TPH1 A779C rs1799913). 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 µl. After PCR amplification, 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 of the HTR2A (T/T, T/C, C/C) and TPH1 polymorphisms. The TPH1 intron 7 A779C and A218C polymorphisms were found to be in 100% linkage disequilibrium (i.e., $r^2 = 1$) and forming three haplotypes A/A, A/C, and C/C. These haplotypes were used in the statistical analyses.

2.3.3. Environmental measures

Maternal nurturance was self-rated by the mothers of the subjects using a scale derived from the Operation Family Study (Makkonen et al. 1981) addressing the emotional significance of the child for the mother. The scale comprises of 4 items ("My child is emotionally important to me"; "I enjoy spending time with my child"; "I am emotionally
important to my child", "My child allows/enables me to fulfill myself"), which were rated on a five point scale ranging from totally disagree (1) to totally agree (5). The Cronbach’s alpha reliabilities for Year 0 and Year 3 nurturance were $\alpha = .66$ and $\alpha = .78$, respectively, and the three-year test-retest Pearson correlation was $r = .37$ ($p < .001$; $r = .52$ after correction for attenuation due to measurement error). The nurturance variable was negatively skewed and was corrected by a cubic root transformation.

**Parental socioeconomic status** was assessed on the basis of two indices: (a) the mother’s and father’s years of education and (b) the annual income of the household (measured on an eight-point scale). The correlation between the mother’s and the father’s years of education was $r = .66$, and the correlation between these two measures and household income was $r = .45$ and $r = .50$, respectively (all $p$ values < .001). The SES indicator was constructed by calculating first the mean of the years of education of the mother and the father and then standardizing the mean into a $Z$ score. Twelve percent of the subjects were living in single-parent households, for whom parental education was determined by the years of education of the single parent. Next, the annual income of the household was standardized into a $Z$ score, and then the $Z$ scores of education and income were summed, resulting in an index of parental socioeconomic status. In order to evaluate the stability of parental SES, it was also assessed in the first follow-up, three years after the baseline. The correlation between baseline and Year-3 parental SES was $r = .94$ ($p < .001$). Given the very high stability, statistical analyses were carried out with the baseline assessment only, for which we had complete data on all the participants.

**Social support** was assessed 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 reliabilities were $\alpha > .90$.

**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 subject 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.” Population density was unevenly distributed and was therefore divided into deciles, and this regressor was used in the analyses. 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. In Year 21 the participants were living in 227 different municipalities around Finland.

2.3.4. Covariates

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

2.4. Statistical analysis

The genetic and environmental main effects and their interactions were analyzed with analysis of covariance (ANCOVA; for categorical independent variables) and linear regression analysis (for continuous independent variables). In linear regression analyses the genes were coded as continuous variables (HTR2A: T/T = 0, T/C = 1, C/C = 2; TPH1: A/A = 0, A/C = 1, C/C = 2). All analyses were controlled for gender, age and the participant’s adulthood years of education.

All the gene–environment interaction models were fitted separately for the HTR2A and TPH1 genes. For maternal nurturance and depressive symptoms, we tested a total of 9 (3 ×
3) separate regression models involving a genotype and maternal nurturance at Year 0, Year 3, and the mean of those scores as independent variables, and depressive symptoms at Year 17, Year 21, and the mean of those scores as dependent variables. For parental SES and harm avoidance, three separate regression models were tested, with the dependent variables being Year-17 HA, Year-21 HA, and the mean of those two measurements. In the study of social support, three separate regression models were tested with the dependent variables being depressive symptoms at Year 17, depressive symptoms at Year 21, and depressive symptoms at Year 21 controlling for depressive symptoms at Year 17 (i.e. depressive symptoms at Year 17 entered as a covariate into the model). The influence of urban/rural residence was examined in a cross-sectional analysis of Year-21 residence and depressive symptoms, and in a longitudinal analysis of Year-17 population density and Year-21 depressive symptoms.
3. RESULTS

The descriptive statistics of the sample are shown in table 1. The correlation between depressive symptoms and HA was $r = .61$ (p < .001) in Year 17 and $r = .59$ (p < .001) in Year 21. The polymorphisms of the HTR2A and TPH1 genes were not associated with each other (p = .35). Regarding the associations between independent environmental variables, the correlation between maternal nurturance and parental socioeconomic status was nonsignificant (Year 0: $r = -.03$, p = .13) or low (Year 3: $r = .09$, p < .001). Adulthood social support was lower in remote rural areas than in other areas (table 3), and correlated positively with maternal nurturance ($r = .08 – .12$, p < .001) and parental SES ($r = .06$, p < .001). High parental SES in childhood predicted more urban adulthood residence ($r = .26$, p < .001), while maternal nurturance was not associated with adulthood residence (p > .05). The following sections present results for the genetic and environmental main effects, and for gene–environment interaction analyses presented separately for the HTR2A and TPH1 genes.

3.1. Genetic main effects

The HTR2A had no main effect on depressive symptoms (Table 2). There was a linear association between HTR2A gene and Year-21 HA, such that the C/C genotype group had the highest and the T/T genotype group the lowest HA. The other findings were in line with this. Even though there were no significant differences in Year-17 HA between genotype groups, the C/C genotype group tended to score slightly higher on HA than the others, and the C/C genotype group had significantly higher mean HA than the others (Table 2). TPH1 was not associated with depressive symptoms or harm avoidance (Table 2).

A gene–environment correlation is present if a gene is associated with an environmental exposure. To test this possibility, we examined the association between the HTR2A and TPH1 with the four environmental measures. The genes were not associated with any of the environmental measures (p values > .05), indicating no gene–environment correlations.
<table>
<thead>
<tr>
<th>Table 1. Descriptive statistics by genotype involved in the analysis</th>
<th>HTR2A</th>
<th>TPH1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of participants†</td>
<td>1246</td>
<td>341</td>
</tr>
<tr>
<td>Women</td>
<td>687 (55.1)</td>
<td>186 (54.5)</td>
</tr>
<tr>
<td>Men</td>
<td>559 (45.9)</td>
<td>155 (45.5)</td>
</tr>
<tr>
<td>HTR2A T102C genotype†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T/T</td>
<td>129 (10.4)</td>
<td></td>
</tr>
<tr>
<td>T/C</td>
<td>548 (44.0)</td>
<td></td>
</tr>
<tr>
<td>C/C</td>
<td>569 (45.6)</td>
<td></td>
</tr>
<tr>
<td>TPH1 haplotype†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>A/A</td>
<td>68 (19.9)</td>
<td></td>
</tr>
<tr>
<td>A/C</td>
<td>170 (49.9)</td>
<td></td>
</tr>
<tr>
<td>C/C</td>
<td>103 (30.2)</td>
<td></td>
</tr>
<tr>
<td>Year-17 Depressive symptoms</td>
<td>44.1 (13.7)</td>
<td>43.7 (13.7)</td>
</tr>
<tr>
<td>Year-21 Depressive symptoms</td>
<td>42.5 (13.8)</td>
<td>41.6 (13.7)</td>
</tr>
<tr>
<td>Year-17 Harm avoidance</td>
<td>91.2 (18.0)</td>
<td>90.9 (18.0)</td>
</tr>
<tr>
<td>Year-21 Harm avoidance</td>
<td>90.0 (18.5)</td>
<td>89.8 (172)</td>
</tr>
<tr>
<td>Year-0 Maternal nurturance</td>
<td>2.1 (0.3)</td>
<td>2.1 (0.3)</td>
</tr>
<tr>
<td>Year-3 Maternal nurturance</td>
<td>2.1 (0.4)</td>
<td>2.1 (0.4)</td>
</tr>
<tr>
<td>Parental SES</td>
<td>0.0 (1.7)</td>
<td>0.0 (1.7)</td>
</tr>
<tr>
<td>Year-17 Social support</td>
<td>2.9 (0.7)</td>
<td>2.8 (0.7)</td>
</tr>
<tr>
<td>Year-21 Social support</td>
<td>2.9 (0.8)</td>
<td>3.0 (0.8)</td>
</tr>
<tr>
<td>Place of residence in Year 21†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Remote rural</td>
<td>193 (15.8)</td>
<td>53 (15.8)</td>
</tr>
<tr>
<td>Rural</td>
<td>226 (18.5)</td>
<td>70 (20.9)</td>
</tr>
<tr>
<td>Sub-urban</td>
<td>560 (45.7)</td>
<td>132 (39.4)</td>
</tr>
<tr>
<td>Urban</td>
<td>245 (20.0)</td>
<td>80 (23.9)</td>
</tr>
<tr>
<td>Year-21 Population density</td>
<td>94.4*</td>
<td>79.4*</td>
</tr>
<tr>
<td>Not living with a partner in Year 21†</td>
<td>379 (31.4)</td>
<td>105 (31.3)</td>
</tr>
<tr>
<td>Unemployed in Year 21†</td>
<td>69 (5.7)</td>
<td>22 (6.5)</td>
</tr>
<tr>
<td>Years of education in Year 21</td>
<td>14.6 (3.0)</td>
<td>14.8 (3.3)</td>
</tr>
</tbody>
</table>

Data are given as mean (SD) unless otherwise indicated
† Data are given as number (percentage) of participants
* Median value of the nontransformed population density (person/km²)

### 3.2. Environmental main effects

Year-3 and Mean maternal nurturance were associated with lower levels of depressive symptoms (Year-0 nurturance: b = -1.67, SE = 1.34, β = -.04, p = .22; Year-3 nurturance: b = -3.42, SE = 1.20, β = -.10, p < .01; Mean nurturance: b = -2.14, SE = .79, β = -.09, p < .01). High parental SES predicted low adulthood HA (Year-17 HA: b = -.96, SE = .33, β = -.09, p = .004; Year-21 HA: b = -1.21, SE = .32, β = -.11, p < .001; Mean HA: b = -1.10, SE = .33, β = -.11, p < .001).
Table 2. Genetic main effects of the T102C polymorphism of the HTR2A genotype and the A779C/A218C haplotype of the TPH1 genotype; Mean (SD)

<table>
<thead>
<tr>
<th></th>
<th>TPH1</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>A/A</td>
<td>A/C</td>
<td>C/C</td>
<td>p</td>
<td>η²</td>
<td></td>
</tr>
<tr>
<td>Year-17 Depressive symptoms (n=285)</td>
<td>44.3 (13.8)</td>
<td>42.9 (14.6)</td>
<td>44.4 (12.2)</td>
<td>0.84</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Year-21 Depressive symptoms (n=323)</td>
<td>43.1 (15.0)</td>
<td>41.0 (13.7)</td>
<td>41.5 (12.9)</td>
<td>0.58</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Mean Depressive symptoms (n=267)</td>
<td>43.1 (12.8)</td>
<td>41.6 (13.1)</td>
<td>42.7 (10.4)</td>
<td>0.26</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Year-17 Harm avoidance (n=285)</td>
<td>91.8 (17.5)</td>
<td>91.9 (18.7)</td>
<td>88.8 (17.2)</td>
<td>0.23</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Year-21 Harm avoidance (n=323)</td>
<td>91.7 (17.4)</td>
<td>89.2 (18.0)</td>
<td>89.6 (15.7)</td>
<td>0.57</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Mean Harm avoidance (n=268)</td>
<td>90.9 (16.8)</td>
<td>90.3 (17.1)</td>
<td>89.0 (14.8)</td>
<td>0.59</td>
<td>-</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>HTR2A</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>T/T</td>
<td>T/C</td>
<td>C/C</td>
<td>p</td>
<td>η²</td>
<td></td>
</tr>
<tr>
<td>Year-17 Depressive symptoms (n=1112)</td>
<td>43.0 (13.6)</td>
<td>44.0 (13.9)</td>
<td>44.5 (13.5)</td>
<td>0.61</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Year-21 Depressive symptoms (n=1250)</td>
<td>41.0 (14.6)</td>
<td>42.8 (13.9)</td>
<td>42.6 (13.5)</td>
<td>0.42</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Mean Depressive symptoms (n=973)</td>
<td>41.3 (12.5)</td>
<td>43.5 (12.6)</td>
<td>43.7 (12.3)</td>
<td>0.26</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Year-17 Harm avoidance (n=1107)</td>
<td>91.0 (18.1)</td>
<td>90.0 (18.5)</td>
<td>91.7 (17.8)</td>
<td>0.41</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Year-21 Harm avoidance (n=1246)</td>
<td>87.3 (18.9)</td>
<td>89.0 (18.3)</td>
<td>91.4 (18.4)</td>
<td>0.02</td>
<td>0.01</td>
<td></td>
</tr>
<tr>
<td>Mean Harm avoidance (n=966)</td>
<td>89.7 (17.1)</td>
<td>89.1 (17.2)</td>
<td>92.1 (16.7)</td>
<td>0.04</td>
<td>0.01</td>
<td></td>
</tr>
</tbody>
</table>

*a Linear contrast p = .027; b C/C > T/T & T/C p = .047

The adulthood education level of the subject was also associated with lower Year-21 HA (b = -.51, SE = .17, β = -.08, p = .003) and Mean HA (b = -.43, SE = .18, β = -.08, p = .017), and there was a tendency in the same direction for Year-17 HA (b = -.29, SE = .18, β = -.05, p = .106). The correlation between parental SES and adulthood education was r = .35 (p < .001). Controlling for adulthood education did not alter the association between parental SES and HA (data not shown).

Social support was associated with depressive symptoms at Year 17 (b = -9.17, SE = .96, β = -.50, p < .001) and at Year 21 (b = -6.36, SE = 1.04, β = -.36, p < .001). Social support at Year 17 did not predict depressive symptoms at Year 21 when depressive symptoms at Year 17 were controlled for (b = -.90, SE = .96, β = -.05, p = .348).

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 3). 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 3).
Table 3. Year-21 measures by place of residence

<table>
<thead>
<tr>
<th></th>
<th>Remote rural</th>
<th>Rural</th>
<th>Suburban</th>
<th>Urban</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Depressive symptoms (M±SD)</td>
<td>44.2 (14.6)</td>
<td>42.5 (13.9)</td>
<td>42.4 (13.4)</td>
<td>41.62 (14.0)</td>
<td>0.28a</td>
</tr>
<tr>
<td>Social support (M±SD)</td>
<td>63.4 (14.5)</td>
<td>68.7 (11.0)</td>
<td>68.0 (12.4)</td>
<td>68.1 (11.9)</td>
<td>&lt;.001a</td>
</tr>
<tr>
<td>Not living with a partner (%)</td>
<td>20.5</td>
<td>20.1</td>
<td>27.9</td>
<td>51.7</td>
<td>&lt;.001b</td>
</tr>
<tr>
<td>Unemployed (%)</td>
<td>5.5</td>
<td>3.6</td>
<td>6.5</td>
<td>4.3</td>
<td>.24b</td>
</tr>
<tr>
<td>Years of education (M±SD)</td>
<td>13.6 (2.8)</td>
<td>14.0 (2.6)</td>
<td>14.8 (3.1)</td>
<td>15.8 (3.1)</td>
<td>&lt;.001a</td>
</tr>
</tbody>
</table>

Note: a Analysis of variance, b Chi square test

The Spearman’s rank correlation coefficient between place of residence and Year-21 population density was r = .60 (p < .001). There was a tendency for higher population density to be associated with lower depressive symptoms in Year 21 (Year 21: b = -.24, SE = .14, β = -.05, p = .08; Year 17: b = -.17, SE = .14, β = -.04, p = .25). Population density was associated with higher social support in Year 21 (b = .36, SE = .12, β = .08, p < .01) but not in Year 17 (b = .03, SE = .12, β = .01, p = .81), and with higher education level (Year 21: b = .22, SE = .03, β = .20, p < .001), higher likelihood of having no partner [Year 21: OR = 1.08 (95% CI = 1.04–1.13), p < .001] and marginally associated with lower likelihood of being unemployed [Year 21: OR = .93 (95% CI = .86–1.01), p = .07].

3.3. Gene–environment interaction effects

3.3.1. HTR2A

Maternal nurturance The effect of the HTR2A genotype × nurturance interaction on depressive symptoms was significant in each of the nine models. Here, the results for the three regression models with the mean depressive symptom scores as the dependent variable are presented (Year 0: b = 4.62, SE = 2.03, p = .023; Year 3: b = 5.01, SE = 1.77, p = .005; Mean: 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; Mean: 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 (all p values > .38).
To further illustrate the interaction effect between HTR2A and nurturance, we categorized the subjects according to level of maternal nurturance (low group = lowest 25% and high group = highest 25% of subjects), and examined the levels of depressive symptoms as a function of the allelic variance of the HTR2A within these two groups (Figure 1). Among subjects with high maternal nurturance, the HTR2A was associated with depressive symptoms (analysis of covariance, with age and gender as covariates: Year 0: p = .07; Year 3: p < .001; Mean: p < .001), while this was not true among subjects with low maternal nurturance in any of the models (all p values > .28). In the group with high maternal nurturance, subjects carrying the T/T or T/C genotype scored significantly lower in depressive symptoms than those with the C/C genotype (effect magnitudes: Year 0: $\eta^2 = .02$; Year 3: $\eta^2 = .08$; Mean: $\eta^2 = .08$).

**Parental socioeconomic status** Next we examined whether the HTR2A gene moderated the association between parental SES and adulthood HA. The interaction effect between HTR2A and SES on HA was statistically or marginally significant in each of the three models (Year-17 HA: $b = .94$, SE = .50, $\beta = .21$, p = .058; Year-21 HA: $b = .99$, SE = .47, $\beta = .22$, p = .035; Mean HA: $b = .90$, SE = .49, $\beta = .22$, p = .065), and showed that high SES predicted low HA in individuals carrying the T/T or T/C genotype (Year-17 HA: $b = -1.36$, SE = .50, $\beta = -.12$, p = .006; Year-21 HA: $b = -1.52$, SE = .46, $\beta = -.14$, p < .001; Mean HA: $b = -1.40$, SE = .49, $\beta = -.14$, p < .004), but not in those carrying the C/C genotype (all p values > 0.38).

**Figure. 1.** Depressive symptoms (Mean ± SE) by HTR2A genotype and maternal nurturance group.
The interaction effect between HTR2A gene and parental SES was further illustrated by categorizing the subjects according to level of childhood SES (low group = lowest 25%, high group = highest 25% of subjects), and examining the levels of HA as a function of the HTR2A within these two groups with analysis of covariance (Figure 1). Among subjects with high SES, the level of HA was linearly dependent on HTR2A, so that the number of C alleles was related to higher HA (Year-17 HA: $p = .029$, linear contrast $p = .044$, $\eta^2 = .03$; Year-21 HA: $p = .012$, linear contrast $p = .017$, $\eta^2 = .03$; Mean HA: $p = .003$, linear contrast $p = .017$, $\eta^2 = .05$). Among subjects with low SES there was some evidence for an association in the opposite direction (i.e. higher HA for T-allele carriers; Figure 2) but this effect was not statistically significant (all $p$ values > .62).

_Urban/rural residence_ The interaction effect between the HTR2A gene and place of residence was statistically significant ($F = 2.13$, df = 6, 1210; $p = .05$; Figure 3) and showed that higher level of urbanicity was associated with lower depressive symptoms in individuals carrying the T/T or T/C genotype (linear contrast $p < .01$, magnitude of effect $\eta^2 = .01$), but not in those carrying the C/C genotype ($p = .49$). The T allele was associated with lower depressive symptoms among individuals living in urban or suburban areas (linear contrast $p = .01$, $\eta^2 = .01$), but with higher depressive symptoms among those living in remote rural areas (linear contrast $p = .03$, $\eta^2 = .03$; Figure 3).
The interaction effect between HTR2A and Year-21 population density was significant when predicting Year-21 depressive symptoms (b = .59, SE = .21, p < .01) and showed that high population density was associated with low depressive symptoms in individuals carrying the T/T or T/C genotype (b = -.51, SE = .20, β = -.10, p = .01), but not in those carrying the C/C genotype (b = .08, SE = .20, β = .02, p = .69). The interaction effect between the HTR2A and Year-17 population density was not statistically significant when predicting depressive symptoms in Year 17 (b = .22, SE = .22, p = .33), although it was in the same direction as the interactions above (T/T or T/C genotype: b = -.28, SE = .20, β = -.06, p = .17; C/C genotype: b = .04, SE = .21, β = .01, p = .86). The HTR2A × Year-17 population density interaction effect was significant when predicting depressive symptoms in Year 21 (b = .50, SE = .21, p = .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 = -.56, SE = .19, β = -.11, p < .01) but not in carriers of the C/C genotype (b = .00, SE = .20, β = .00, p = .99).

We also 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 × place of residence was still marginally significant (p = .06) and the HTR2A × Year-21 population density interaction effect was significant (b = .49, SE = .20, p = .01).

**Social support** There was no significant interaction effect between the HTR2A and social support on Year-17 or Year-21 depressive symptoms (p values > .05).

### 3.3.2. TPH1

**Maternal nurturance and parental socioeconomic status** There was no significant interaction effect between TPH1 haplotype and maternal nurturance on depressive symptoms or between TPH1 and parental SES on harm avoidance (p values > .05).

**Social support** The interaction effect between TPH1 and social support at Year 17 was statistically significant when predicting depressive symptoms at Year 17 (b = 3.00, SE = 1.42, β = .50, p = .038) and at Year 21 (b = 4.61, SE = 1.55, β = .79, p = .003), showing that while social support was associated with depressive symptoms in each of the genotype groups, the association was stronger the more A alleles individuals were carrying (Year-17: A/A: b = -13.08, SE = 2.26, β = -.66, p < .001; A/C: b = -9.27, SE = 1.44, β = -.50, p < .001; C/C: b = -6.78, SE = 1.63, β = -.40, p < .001; Year-21: A/A: b = -14.19, SE = 2.70, β = -.66, p < .001; A/C: b = -6.01, SE = 1.49, β = -.35, p < .001; C/C: b = -3.13, SE = 1.78, β = -.19, p = .083). The interaction effect was illustrated by plotting the model-predicted depressive symptoms at Year 21 against social support by TPH1 haplotype groups (Figure 4).

Next we examined whether the interaction between TPH1 and social support predicted a change in depressive symptoms over time. This was studied by using TPH1, social support, and their interaction effect to predict depressive symptoms at Year 21, with depressive symptoms at Year 17 entered as a covariate into the model. The interaction effect between TPH1 and social support was significant (b = 2.54, SE = 1.27, β = .44, p = .047) and indicated that low social support predicted an increase in depressive symptoms over time.
only among subjects carrying the A/A haplotype (A/A: $b = -9.27$, $SE = 3.29$, $\beta = -.45$, $p = .005$; A/C: $b = .19$, $SE = 1.25$, $\beta = .01$, $p = .88$; C/C: $b = .35$, $SE = 1.58$, $\beta = .02$, $p = .82$). The difference in regression coefficients between the A/A haplotype group and others was considerably larger when predicting the change in depressive symptoms than in the other two regression analyses, suggesting the possibility of a statistical artifact. However, we did not detect any outliers (as identified by extreme z-scores, Mahalanobis distance and Cook’s distance) in any of the genotype groups that would have had considerable influence on the regression coefficients.

Urban/rural residence There was a significant interaction effect between the TPH1 haplotype and Year-21 urban/rural residence on Year-21 depressive symptoms ($p = .011$; Figure 5A) indicating that living in remote rural area was associated with high depressive symptom scores in individuals carrying the A/A genotype ($p = .024$) but not in others ($p$ values > .05), although the association was into the same direction in rural as in remote rural area (see figure 5A). However, the group responsible for this effect was relatively small (A/A carriers in remote rural area $n = 10$).
Figure 5. The interaction effect between TPH1 and residence on depressive symptoms (panel A) and social support (panel B).

Given the moderating role of the TPH1 in social support and the lower social support in remote rural areas, we assessed if the TPH1 moderated the association between urban/rural residence and perceived social support. There was a significant interaction effect between TPH1 and rural residence in predicting Year-21 social support (p = .028; Figure 5B) indicating that rural residence was associated with low social support in individuals carrying the A/A haplotype (linear contrast p = .027) but not in others (p > .05).

Analyses of the TPH1 × residence with population density provided provisional support for the TPH1 × residence interaction: There was a marginally significant TPH1 × Year-17 population density interaction (p = .065) when predicting Year-21 depressive symptoms but not when predicting Year-17 depressive symptoms (p = .174). The TPH1 × Year-21 population density interaction was also significant when predicting Year-21 depressive symptoms (p = .008). Controlling for social support, unemployment or marital status did not substantially alter this interaction effect, although controlling for social support did reduce the effect somewhat (data not shown).
4. DISCUSSION

The present findings indicate that variations in the T102C polymorphism of the serotonin receptor 2A (HTR2A) gene may determine, in part, how individuals are influenced by early life experiences and adulthood social circumstances. Exposure to high childhood maternal nurturance predicted low adulthood depressive symptoms in individuals carrying the T/T or T/C genotype but not in those carrying the C/C genotype. Similarly, high parental SES in childhood predicted low adulthood harm avoidance in T/T or T/C genotype carriers but not in C/C genotype carriers. The HTR2A was also involved in how adulthood urban/rural residence predicted differences in depressive symptoms. Urban residency was associated with lower depressive symptoms in individuals carrying the T/T or T/C genotype, while residential differences had no effect among individuals carrying the C/C genotype. The HTR2A did not moderate the influence of social support.

The A779C/A218C haplotype of the TPH1 gene did not moderate the influence of childhood maternal nurturance or parental SES, but it did moderate the impact of adulthood social support and urban/rural residence on depressive symptoms, such that low social support and remote rural residence were related to depressive symptoms most strongly in individuals carrying A alleles of the TPH1 haplotype than in others. This was particularly true for individuals carrying the A/A haplotype. Furthermore, rural residence was associated with low social support in individuals carrying the A/A haplotype but not in others.

These findings indicate that the HTR2A and TPH1 genes may be involved in gene–environment interactions that influence individual differences in depressive symptoms and temperament. However, interactions between genes and environments are not explanations for behavior but rather something to be explained (Rutter & Pickles 1991). They provide information on the role of genetic variants in sensitivity to environment and how these sensitivities may shape individual developmental pathways.
4.1. Serotonin receptor 2A

Early life experiences in humans and non-human primates have been shown to induce long-term alterations in serotonergic functioning which, in turn, may be associated with individual stress vulnerability (Sánchez et al. 2001). For instance, child abuse has been shown to alter serotonergic functioning (Kaufman et al. 1998), and rhesus macaques raised in adverse rearing conditions exhibit serotonergic dysfunctions and heightened behavioral and neuroendocrinological reactions to stress (Bennett et al. 2002, Barr et al. 2004; see also Arborelius et al. 2000). With respect to 5-HT$_{2A}$ functioning, Pine et al. (1996) found that exposure to harsh parenting was inversely related to the density of 5-HT$_{2A}$ platelet receptors in a sample of adolescent boys, providing evidence for a role of 5-HT$_{2A}$ receptors in mediating the impact of environmental risks.

The HTR2A gene determined whether exposure to high maternal nurturance and high childhood SES predicted low adulthood depressive symptoms and harm avoidance. Compared to T/T or T/C genotype carriers, the C/C genotype carriers had higher depressive symptoms and harm avoidance irrespective of a beneficial childhood environment. In other words, carriers of the C/C genotype were insensitive to the positive influence of these environmental exposures. When the participants were stratified by childhood environments, the HTR2A gene was associated with low depressive symptoms and low harm avoidance among participants with high childhood maternal nurturance and high parental SES, but not among those with low nurturance and low parental SES.

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 (Turkheimer et al. 2003; see Shanahan & Hofer 2005). For instance, the heritability of cognitive abilities has been shown to be higher among children of families with high socioeconomic status (SES) than those of low-SES families (Harden et al. 2007, Turkheimer et al. 2003). Following this line of reasoning, we suggest that the HTR2A is associated with individual differences in responsivity to positive childhood environmental influences and that in this context it may function as an “opportunity gene” as opposed to a “risk gene”. That is, the allelic variance of the HTR2A may be associated with an ability to utilize positive aspects of the environment – in the
present case supportive mothering and high childhood SES – rather than with heightened vulnerability to detrimental influences.

The moderating role of the HTR2A extended beyond childhood environment to adulthood urban/rural residency. Depressive symptoms tended to be higher and perceived social support was lower in remote rural areas than in urban areas, suggesting that Finnish urban residency may provide more opportunities for psychosocial well-being than residency in remote rural areas, although the regional differences were small (cf. Joukamaa et al. 2003). The HTR2A–residence interaction indicated that urban residence predicted low depressive symptoms in individuals carrying the T/T or T/C genotype but not in those carrying the C/C genotype, again suggesting insensitivity of the C/C genotype carriers to beneficial environmental circumstances. Moreover, the direction of the allelic association between T102C polymorphism and depressive symptoms was the opposite in different residential areas: the T allele was associated with low depressive symptoms in urban and suburban areas but with high depressive symptoms in remote rural areas.

Previous studies have identified the C allele as a risk allele for psychiatric disorders. A recent meta-analysis (Abdolmaleky et al. 2004) concluded that there is an association between the C allele of the T102C polymorphism of the HTR2A gene and increased risk of schizophrenia. 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, Zhang et al. 1997). The present findings imply that the association between C allele and risk of psychiatric disorder may be due to the C-allele carriers’ insensitivity to positive aspects of early developmental environment and current social conditions. Moreover, the association between the HTR2A and psychiatric disorders may be expressed differently in response to different social circumstances, e.g., childhood environment or urban/rural residence. The inconsistent results from previous studies may thus be due to the omission of relevant environmental factors moderating the impact of the HTR2A.

With respect to the neuropsychological mechanisms involved, a path via the prefrontal cortex might be hypothesized (see Deakin 1996). The prefrontal cortex is involved in
cognitive control and regulation of negative emotions (Miller 2000, Ochsner et al. 2002), among other functions, and its dysfunctions have been implicated in depression (Rogers et al. 2004). The 5-HT$_{2A}$ receptors are found in the prefrontal cortex (van Heeringen et al. 2003; see Deakin, 1996), and their binding potential has been associated with depression (Oquendo and Mann 2001, Sheline et al. 2004, Yatham et al. 2000) and related personality traits (Moresco et al. 2002, van Heeringen et al. 2003). Anxiety sensitivity has also been associated with the 5-HT$_{2A}$ receptors in humans and mice (Moresco et al. 2002, Weisstaub et al. 2006). These factors might play a role in the differential responsivity to environmental circumstances.

4.2. Tryptophan hydroxylase 1

Current social conditions have been linked with endocrionological and physiological functioning in humans and non-human primates. Low socioeconomic status (Matthews et al. 2000) and social support (Iy et al. 1993; see also Oehler et al. 1987, Uchino et al. 1996) have been shown to influence serotonin functioning. A recent study (Manuck et al. 2005) found that low neighborhood socioeconomic status (SES) predicted low serotonin functioning even when the participant’s own SES was taken into account. Social status is also associated with serotonin turnover in monkeys (Kaplan et al. 2002), and social stress may impair serotonergic function in the prefrontal cortex (Fontenot et al. 1995).

In the present study the correlation between low social support and high depressive symptoms was strongest among individuals carrying A alleles of the A779C/A218C haplotype of the TPH1 gene, suggesting that those people may be most vulnerable to the lack of social support. A/A haplotype carriers living in remote rural areas also had higher depressive symptoms and lower social support than those carrying other haplotypes. These findings are in line with the results of previous research that has identified the A allele as the risk allele of suicidal behavior (Rujescu et al. 2003, Bellivier et al. 2004), low serotonin levels (Jönsson et al. 1997), and poorer response to the psychopharmacological treatment of depression (Peters et al. 2004; Serretti, Zanardi et al. 2001). Our finding therefore suggests that the A allele of the A779C/A218C haplotype may increase the sensitivity of the serotonergic system to social influences.
In a previous study with the same sample as here but with different measures, Keltikangas-Järvinen et al. (2006) found an interaction effect between the TPH1 haplotype and hostile childhood family environment in predicting adulthood harm avoidance, such that individuals carrying the A/A haplotype were most vulnerable to a hostile family environment. The present study found no evidence for a moderating role of the TPH1 involving childhood maternal nurturance or parental socioeconomic status. The differences between the study of Keltikangas-Järvinen et al. (2006) and present findings may be due to our relatively small sample size of the TPH1-genotyped participants, which leads to limited power to observe interaction effects. Replication studies with larger samples are needed to clarify the role of the TPH1 in moderating the influence of childhood environments.

Recently a second isomorphism of the TPH gene, viz. TPH2, was discovered. Studies on rodents (Patel et al. 2004, Walther et al. 2003, Zhang et al. 2004) suggest that TPH2 is the primary isomorphism involved in the synthesis of serotonin in the central nervous system, while TPH1 is primarily expressed peripherally (e.g. in the duodenum) and only in small amounts in the brain (e.g. in the pineal gland). The second isomorphism, also referred to as neuronal TPH, has therefore been considered as a more promising candidate gene than TPH1. Recent studies have associated TPH2 with major depression (Zhou et al. 2005, Zill et al. 2004), bipolar disorder (Harvey et al. 2004), schizophrenia (De Luca 2005) and suicidal behavior (Zhou et al. 2005). The TPH2 has also been linked with serotonin turnover (Zhou et al. 2005), and at least two brain imaging studies (Brown et al. 2005, Canli et al. 2005) have demonstrated that the gene may be associated with amygdala reactivity toward emotional stimuli. However, the functional significance of the TPH2 polymorphisms remains to be determined (see Zhou et al. 2005).

Although the discovery of TPH2 has lead some researchers to argue that only this TPH isomorphism is important for the functioning of the central nervous system (Shaltiel et al. 2005), the most recent available evidence suggests that this conclusion may be premature. A human postmortem study (Zill et al. 2007) found that both TPH1 and TPH2 are expressed in several areas of the brain. While TPH2 mRNA was more abundant in the raphe nuclei, TPH1 mRNA was more abundant in the hypothalamus and amygdala. In addition, Nakamura et al. (2006) found in rodents that TPH1 was associated with brain
serotonin levels during late development, but not in adults. This finding suggests that TPH1 may be involved in the development of serotonergic neurons which, in turn, is likely to have an influence on adult behavior (see Gaspar et al. 2003).

4.3. Gene–gene interactions and gene–environment correlations

We have interpreted our findings as gene–environment interaction effects. However, twin studies have demonstrated that factors traditionally believed to be environmental may, in fact, include heritable variance (Plomin & Bergeman 1991). Measures of socioeconomic status (Rowe et al. 1998, Silventoinen et al. 2000), parenting (Spinath & O’Connor 2003, Losoya et al. 1997, Kendler et al. 1997, Perusse et al. 1994), social support (Kessler et al. 1992, Wade & Kenlder 2000, Kendler 1997), and even place of residence (Whitfield et al. 2005) may all be partly heritable. It is therefore possible that the interaction effects reported here might reflect gene–gene rather than gene–environment interactions. In other words, parents may transmit an as yet unknown gene that is associated with, say, maternal nurturance, to their child, and this gene might then interact with the gene of interest, e.g., the HTR2A, to produce differences in temperament or depressive symptoms.

In light of the current evidence, a gene–environment rather than gene–gene interpretation appears more likely, since a similar interaction effect was observed with different environmental variables. In the case of HTR2A, the measures of maternal nurturance, parental SES, and urban/rural residence were largely independent of each other, making it unlikely that there is an unknown gene associated with them all and interacting with the HTR2A. Regarding social support and TPH1 gene, it is possible that the causal relation between social support and depression is bidirectional, i.e. depression may lead to reduced support (Stice et al. 2004). However, the TPH1 had no significant main effects on depressive symptoms or social support, but it moderated the association of social support with depressive symptomatology over time. Furthermore, urban/rural residence provided evidence for an interaction effect similar to that produced by social support.

In sum, we believe that the present findings may be interpreted as gene–environment interactions rather than gene–gene interactions. However, the possibility of gene–gene interactions should not be dismissed. Future studies should evaluate gene–environment
interactions involving the HTR2A and TPH1 with a variety of environmental exposures and
gene–gene interactions with other genes in order to further assess these two possibilities.
For instance, the HTR2A has been found to interact with COMT in determining personality
trait absorption (Ott et al. 2005; see also Kaufman et al. 2006). Gene–environment
correlations in which a gene is associated with an environmental variable should also merit
further attention in molecular genetics of behavior (see Jaffee & Price 2007).

4.4. Developmental pathways

The identification of gene–environment interactions may give clues to the developmental
pathways underlying the phenotype of interest. The findings of the present study indicate
that early experiences may be important in the behavioral expression of the HTR2A
variance, and it would be of interest to study whether the HTR2A is associated 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 (ADHD) and oppositional defiant disorder (ODD)
early in life (Capaldi 1992, Ostrander et al. 2006). On the other hand, adulthood depression
may be preceded by anxious childhood temperament and internalizing behavior (Caspi et
al. 1996, Zahn-Waxler et al. 2000). Other developmental pathways to adulthood depression
are also possible (Kendler et al. 2002, 2006).

Social support has been shown to influence health directly by being beneficial in itself
and indirectly by protecting from the consequences of negative life events (Cohen & Wills
1985). We examined only the direct influence of social support, but future research should
extend investigations to include three-way interactions between TPH1 gene, life events, and
social support. For example, Kaufman et al. (2004) found that the 5-HTTLPR
polymorphism moderated the influence of maltreatment on depression in children, and that
this interaction effect was further moderated by the availability of social support.
Maltreated children with the s/s genotype and no social support had higher depression
scores than maltreated children with the s/s genotype who had adequate social support.

Urban/rural residence was the only environmental factor that interacted with both the
HTR2A and TPH1 genes, indicating that community-level factors may provide valuable
information on how environmental context affects biological processes. 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). The present study adds to the neighborhood 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. More detailed data on neighborhood characteristics are needed to identify the causal mechanisms underlying the effect of urban/rural residence on depressive symptoms.

Future studies examining the developmental pathways connecting the HTR2A and TPH1 genes to depression should also consider the role of other phenotypes associated with these genotypes. Tryptophan is involved in social behaviors such as social dominance and aggressive behavior (Moskowitz et al. 2000), and the TPH1 gene has been associated with impulsive and aggressive tendencies (Hennig et al. 2005, Manuck et al 1999, New et al. 1998, Rujescu et al 2002, Staner et al. 2002) and with schizophrenia (Hong et al. 2001, Li & He 2006, Sekizawa et al. 2004). The binding potential of 5-HT2A receptors has been associated with impulsive aggression (Coccaro et al. 1997; see also Peremans et al. 2003) and schizophrenia (Abdolmaleky et al. 2004). These associations suggest that a developmental path via emotion dysregulation and externalizing behavioral problems (Capaldi 1992, Ostrander et al. 2006; see above) might be involved in the associations between the HTR2A and TPH1 genotypes and depression.

4.5. Methodological considerations

The present study has several methodological strengths. First, the participants were from a representative population-based sample. The sample size was relatively large in analyses involving the HTR2A gene, but considerably smaller in those of the TPH1 gene. Second, all analyses applied a prospective longitudinal study design in addition to cross-sectional analyses applied in studies of adulthood environments. Third, the outcome measures of depressive symptoms and harm avoidance were assessed in two test settings taken four years apart, which reduced the role of measurement error and allowed us to assess the
robustness of the findings. Our results were largely replicated with data from both test settings.

Fourth, the environmental factors were measured in a reliable manner. As maternal nurturance was reported by the participant’s mother in childhood, it was not confounded by measurement biases arising from retrospective assessment or from the use of a common informant. Assessment of parental SES was also based on parents’ reports and showed very high stability across a three-year period. Urban/rural residency was determined on the basis of a self-reported assessment and an objectively determined measure of population density, both of which provided evidence for similar interaction effects. Social support was assessed on the basis of only one single self-report instrument, which introduced the possibility of common informant confounding, since both the independent and dependent variables were reported by the participants. On the other hand, an individual’s perception of available support may be psychologically relevant in its own right.

Despite the methodological strengths, it must be noted that even relatively robust findings of molecular genetic associations from a single sample need to be interpreted with caution pending replication in independent samples. We hope that the present findings will lead other research groups to further explore the moderating roles of the HTR2A and TPH1 in additional study samples.

4.6. An evolutionary afterthought

Finally, we wish to note a fundamental theoretical issue which has received little attention in behavioral genetic research and which was not touched upon in the present study either. Most genetic studies of behavior to date have investigated mainly how genetic variants are related to psychiatric disorders and other maladaptive traits and behaviors. While it is understandable that psychiatric and medical genetics are interested mainly in polymorphisms associated with diseases, we believe that behavioral genetics should be considered from an evolutionary point of view. Allele distributions are determined by forces of evolution, particularly by natural selection. It would be rather surprising if evolution had maintained, say, the C allele of the HTR2A T102C polymorphism in the
population just to make people more vulnerable to depression, schizophrenia, impulsive aggression and other apparently disadvantageous traits.

Empirical evidence pertaining to this issue is scarce, and it is beyond the present discussion to consider thoroughly the theoretical questions related to the evolutionary significance of heritable individual differences (see Buss & Greiling 1999, Nettle 2006). However, recent developments in behavioral ecology of personality may advance our knowledge in this respect (Carere & Eens 2005, Dall et al. 2004, Sih et al. 2004). For example, Cochran et al. (2005) have argued that the impact of adverse childhood environment on the development of defensive mechanisms (e.g. stress and threat reactivity) should not be understood as a developmental impairment but rather as an evolutionary adaptive response against a risky environment in which high vigilance and constant preparedness are required.

From this viewpoint, the present findings might be interpreted as differential phenotypic plasticity in response to different environmental circumstances. However, on the basis of the present study, it is not possible to say whether or not this has adaptive significance in an evolutionary sense. It is, of course, quite possible that a great deal of allelic variance in common polymorphisms associated with deleterious psychological traits is evolutionarily neutral. Nevertheless, future studies should investigate whether the HTR2A, TPH1 and other genes are related to evolutionarily relevant traits, such as reproductive behavior or disease resistance. This may open up new avenues for molecular genetic research on human behavior.

4.7. Conclusions

Molecular genetic research applying simple association studies has provided mostly inconsistent evidence for the role of specific genes in the development of temperament and psychiatric disorders (Hamer 2002, Ebstein 2006). More recent studies (e.g. Berman & Noble 1997, Caspi et al. 2002, 2003; Ozkaragoz & Noble 2000) have begun to explore the interaction effects between genes and environments (see Caspi & Moffitt 2006, Ebstein 2006, Lesch 2004). The present findings add to this literature. Here main effects of the serotonin receptor 2A (HTR2A) and tryptophan hydroxylase 1 (TPH1) genes were either
absent or inconsistent. However, gene–environment interaction effects indicated that the
HTR2A and TPH1 genes may be involved in determining individual differences in
depressive symptoms and harm avoidance by moderating depressogenic environmental
influences. Such interactions were observed with measures of childhood environment, i.e.,
maternal nurturance and parental SES, and adulthood social circumstances, i.e., social
support and urban/rural residence. The present findings thus provide support for the
argument that molecular genetic studies of human behavior will produce more consistent
results when environmental exposures are taken into account.

It also bears emphasizing that the interplay between genes and environments is a two-
way street. Gene–environment interactions are relevant not only to behavioral genetics but
also to environmentally oriented psychological research (Shostak 2003). Just as it is
necessary to include environmental measures in genetic study designs, it is necessary to
consider the role of genes in modifying the role of environmental influences. Individuals
differ genetically in their sensitivity to social environments, and understanding these
differences should advance our understanding of the role of environment in psychological
and social development.
ACKNOWLEDGMENTS

I am indebted to all the people who have been involved in designing and collecting data in the Cardiovascular Risk in Young Finns study. My work would – literally – have been impossible without them.

I am grateful to my supervisor, Professor Liisa Keltikangas-Järvinen, for the opportunity of getting involved in the Young Finns study. She has set a high standard for research and provided support and freedom for a curious mind, which I greatly appreciate.

Professor Mika Kivimäki has been an indispensable mentor in the art of manuscript sculpting. Discussions with Docent Marko Elovainio have been most helpful in clarifying what one should and should not do in science. Working with these two fellows has been as joyful as it has been enlightening.

I wish to thank Professors Matti Virkkunen and Jaanus Harro for reviewing my thesis and offering helpful comments on it. I also wish to thank all my co-authors and my colleagues at the Department of Psychology for all the help they have provided.

All this work would have made me a dull boy if it hadn’t been for a very special person, Vappu Ylinen. More often than not, it has been delightful to find her luring me away from the computer. Finally, I wish to express my gratitude to my mother, Aino Mesiäislehto, for the hereditary elements and nurturance that have guided me and my three siblings to the paths of higher education.

My scholarly interests were financially supported by Otto A. Malm Foundation, Helsinki University Science Foundation, and Finnish Cultural Foundation. Their support is gratefully acknowledged.
REFERENCES


Souery D, Mendlewicz J. (2000). 5-HT2a receptor polymorphism gene in bipolar disorder and 
harm avoidance personality trait. American Journal of Medical Genetics Part B: 
Neuropsychiatric Genetics, 96, 360–364.

Blazer D, George LK, Landerman R, Pennybacker M, Melville ML, Woodbury M, Manton KG, 
Psychiatry, 42, 651–656.

Blazer DG, Kessler RC, McGonagle KA, Swartz MS. (1994). The prevalence and distribution of 
major depression in a national community sample: the National Comorbidity Survey. American 

type A behavior, and coronary artery disease. Psychosomatic Medicine, 49, 331–340.


Booij L, Van der Does AJ. (2007). Cognitive and serotonergic vulnerability to depression: 

receptors in prefrontal cortex enhances dopaminergic activity. Journal of Neurochemistry, 95, 
1597–1607.


Bradley RH, Corwyn RF. (2002). Socioeconomic status and child development. Annual Review of 

locus does not contain common polymorphism affecting mRNA levels in adult brain. Molecular 
Psychiatry, 9, 109–114.

55–71.

regulatory variant of the human tryptophan hydroxylase-2 gene biases amygdala reactivity. 
Molecular Psychiatry, 10, 884–888.


T102C polymorphism in 5HT2A and schizophrenia plus identification of new polymorphisms in
the promoter. *Molecular Psychiatry, 3*, 42–49.

Stice E, Ragan J, Randall P. (2004). Prospective relations between social support and depression:

Stover E, Fenton W, Rosenfeld A, Insel TR. (2003). Depression and comorbid medical illness: The


polymorphism in the promoter region of the tryptophan hydroxylase gene is associated with
alcohol dependence in an aboriginal group in Taiwan. *Alcoholism: Clinical and Experimental
Research, 29*, 1–7.

Sundquist K, Frank G, Sundquist J. (2004). Urbanisation and incidence of psychosis and

Suomi SJ. (2005). Mother-infant attachment, peer relationships, and the development of social


Taylor SE, Lerner JS, Sage RM, Lehman BJ, Seeman TE. (2004). Early environment, emotions,

Health and Social Behavior, 36*, 53–79.

by serotonin receptor 2A genetic variation in postmortem brain samples from subjects who did


Uchino BN, Cacioppo JT, Kiecolt-Glaser JK. (1996). The relationship between social support and
physiological processes: A review with emphasis on underlying mechanisms and implications

77


