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Interpersonal relationships and behaviour: moderation by functional gene variants

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Is life just a game where we make up the rules
While we're searching for something to say
Or are we just simply spiralling coils
Of self-replicating DNA?

Monty Python
The Meaning Of Life

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LIST OF ORIGINAL PUBLICATIONS

I Paaver, M., Kurrikoff, T., Nordquist, N., Oreland, L., Harro, J. (2008). The effect of 5-HTT gene promoter polymorphism on impulsivity depends on family relations in girls. Progress in Neuro-Psychopharmacology & Biological Psychiatry, 32(5), 1263–1268.

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III Reif, A., Kiive, E., Kurrikoff, T., Paaver, M., Herterich, S., Konstabel, K., Tulviste, T., Lesch, K.P., Harro, J. (2011). A functional *NOS1* promoter polymorphism interacts with adverse environment on functional and dysfunctional impulsivity. Psychopharmacology, 214(1), 239–248.

IV Kurrikoff, T., Lesch, K.-P., Kiive, E., Konstabel, K., Herterich, S., Veidebaum, T., Reif, A., Harro, J. (2012). Association of a functional variant of *NOS1* with personality, anxiety and depressiveness. Development and Psychopathology, 24, 1225–1235.

V Kiive, E., Kurrikoff, T., Mäestu, J., Harro, J. (2010). Effect of α2A-adrenoceptor C-1291G genotype and maltreatment on hyperactivity and inattention in adolescents. Progress in Neuro-Psychopharmacology & Biological Psychiatry, 34(1), 219–224.

Contribution of the author

The author of the present dissertation contributed to the publications as follows:
- for **Paper I**, creating a psychological measure for the paper – Tartu Family Relationships Scale, contribution to writing the manuscript
- for **Paper II**, helping to recruit the sample, conducting the data analysis, and writing the manuscript as the main author
- for **Paper III**, helping to recruit the sample for the follow-up in 2007 and conducting some testing for the same sample, conducting most of the data analysis, contribution to writing the manuscript
- for **Paper IV**, helping to recruit the sample for the follow-up in 2007 and conducting some testing for the same sample, conducting most of the data analysis, and writing the manuscript as the main author
- for **Paper V,** contribution to writing the manuscript

ABBREVIATIONS

ADHD	attention-deficit hyperactivity disorder
ADRA2A	α_{2A}-adrenoceptor gene
AMIS	Adaptive and Maladaptive Impulsivity Scale
BIS	Barratt Impulsiveness Scale
CNS	central nervous system
DNA	deoxyribonucleic acid
ECPBHS	Estonian Children Personality, Behaviour and Health Study
G × E	gene-by-environment interactions
l	long
l/l	long/long
mRNA	messenger ribonucleic acid
nNOS	neuronal nitric oxide synthase
NO	nitric oxide
NOS	nitric oxide synthase
NOS1	neuronal nitric oxide synthase
NOS1	neuronal nitric oxide synthase gene
NOS1 Ex1f-VNTR	a repeat polymorphism in the promoter region of *NOS1* exon 1f
PARQ/Control	Parental Acceptance-Rejection/Control Questionnaire
PCR	polymerase chain reaction
s	short
s/l	short/long
s/s	short/short
SLC6A4	serotonin transporter gene
SLE	stressful life events
SNAP-IV	Swanson, Nolan and Pelham Questionnaire IV
5-HT	serotonin
5-HTT	serotonin transporter
5-HTTLPR	serotonin transporter gene-linked polymorphic region

1. INTRODUCTION AND REVIEW OF LITERATURE

"Give me a dozen healthy infants, well-formed, and my own specified world to bring them up in and I'll guarantee to take any one at random and train him to become any type of specialist I might select – doctor, lawyer, artist, merchant-chief and, yes, even beggar-man and thief, regardless of his talents, penchants, tendencies, abilities, vocations, and race of his ancestors" – this is a famous sentence written by behaviourist John Broadus Watson about 80 years ago. Although admitting that he was "going beyond my facts", this represents a view that environment has a major impact on human behaviour. Still, there must be something more to influence our behavioural tendencies as twins growing up in a different families with different environment often show behavioural similarities (Kim, 2009). Already the ancient Greeks held that humans inherited qualities, including behavioural ones, from their ancestors. Thus in Book IV of Homer's *Odyssey*, Menelaus greets two young visiting strangers, "Ye are of the line of men that are sceptred kings . . . for no churls could beget sons like you" (Kim 2009, p.3). Contemporarily, it is generally accepted that both inherited and environmental factors spawn differences in human cognitive and behavioural traits (Lenroot & Giedd, 2011), although we are still on our way to figure out, which genes are associated with which behaviour, what kind of environmental conditions play a role in gene-environment interaction and how genes and environment are interacting.

1.1. Impulsivity and anxiety related traits in psychiatric disorders

The treatment of people with mental illnesses in the cabin of peasant in some European countries two centuries ago was sometimes quite simple – "When a strong man or woman gets a complaint, the only way they have to manage is by making a hole in the floor of the cabin, not high enough for the person to stand up in, with a crib over it to prevent his getting up. They give this wretched being his food there, and there he generally dies" (Shorter, 1997, p.1). This type of treatment of troublesome mentally ill men or women was quite common in the past and was not led by the cruelty, but by the lack of knowledge in the causes and cure of mental disorders. Nowadays we have considerably better treatment of psychiatric disorders, but there is still much space for further development. One way to create deeper understanding of neurobiology of human behaviour leading to disorders is through gaining more information about which genes are associated with traits related to psychiatric disorders.

Psychiatric disorders are quite complex and therefore traits underlying psychiatric disorders are assumed to have simpler genetic underpinnings than disorders themselves (Caspi & Moffitt, 2006). A trait, that associates with many

psychopathologies, including attention-deficit hyperactivity disorder (ADHD), Cluster B personality disorder, substance use disorders, and mania is impulsivity (Reif et al., 2009).

Although there are many ways to define impulsivity, it is generally considered as a disposition not to deliberate much before reacting to external or internal stimuli, associated with a risk to get involved in troubles, accidents, and fights (Moeller et al., 2001). Representative first-person statements characterizing impulsivity include "I will often say whatever comes into my head without thinking first" and "Often I do not spend enough time thinking over the situation before I act". Dickman (1990) named such thoughtless behaviour dysfunctional impulsivity, reflecting the situational inappropriateness of hasty responses. However, increased impulsivity still remains within the behavioural repertoire of the human population, and we can assume that inherited tendencies to respond quickly to environmental changes might be adaptive in some instances. For example, quick response is needed in suddenly breaking and maneuvering a car in order to avoid an object on the road. Secondly, excessively delaying of an action may lead to missed opportunities and thus, accuracy should be sacrificed to gain speed if correct responses have greater value than errors (Mulder et al., 2010). Acting with relatively little forethought in situations where it is optimal, was named functional impulsivity by Dickman (1990). However, in impulsivity related disorders, it is mostly the construct of dysfunctional impulsivity that is borne in mind.

For example, dysfunctional impulsivity is characteristic to attention-deficit hyperactivity disorder (Morgan & Norris, 2010), a disorder affecting 5% of children in Europe (Wittchen et al., 2011) and manifesting with inattention, poor impulse control and hyperactivity. It begins in childhood and causes impairment of school performance, intellectual functioning, social skills, car driving, and occupational functioning (Faraone et al., 2005). Impulsiveness also features in anxiety disorders (Perugi et al., 2011) as well as in depression (Acremont & Linden, 2007; Granö et al., 2007; Hutchinson et al., 1998). It is conceivable that impulsive individuals are more prone to confront adverse life events which in turn act as triggers for depression. In a longitudinal study with depressed in-patients both impulsivity and depression scores decreased with treatment (Corruble et al., 1999). Therefore, impulsivity might be partly state dependent, increasing with depressivity and decreasing after a normal emotional state is achieved.

Depression is a severe mental disorder with estimated 12-month prevalence of 6.9% in EU, thus being one of the most frequent mental disorders (Wittchen et al, 2011). It is characterized by a loss of interest and an inability to experience pleasure. Most depressed patients express feelings of hopelessness, worthlessness, sadness, guilt, and desperation and they frequently exhibit loss of appetite, insomnia, crying, diminished sexual desire, loss of ambition, fatigue, and either motor retardation or agitation (Meyer & Quenzer, 2005). Thus, depression is an etiologically heterogeneous group of brain disorders

characterized by a wide range of symptoms that reflect alterations in cognitive, psychomotor and emotional processes. Affected individuals differ remarkably regarding the profile of clinical features, severity and course of illness as well as their response to drug treatment and reintegration efforts (Lesch, 2004).

Depression is associated with anxiety-related traits, including neuroticism (Kendler et al., 1995; Thapar et al., 1997). According to Spielberger (Spielberger, 1966), there are two kinds of anxieties: state anxiety and trait anxiety. State anxiety reflects a transitory emotional state or a condition that is characterized by subjective, consciously perceived feelings of tension and apprehension, and heightened autonomic nervous system activity. It may fluctuate and can vary in intensity. In contrast, trait anxiety refers to a general tendency to respond with anxiety to perceived threats in the environment, and is a relatively stable characteristic of an individual. Trait anxiety has strong correlations with neuroticism (Scheier et al., 1994) that captures an individual's chronic tendency to experience negative thoughts and feelings (John & Srivastava, 1999). As a broad trait, neuroticism comprises the characteristics of anxiety, anger–hostility, depression, self-consciousness, impulsivity, and vulnerability (Costa & McCrae, 1992). Key to Costa and McCrae's conceptualization of neuroticism is that it captures individual variation in psychological resilience such that individuals high in neuroticism are more vulnerable to emotional distress (Kling et al., 2003) and, in contrast, those low in neuroticism are better able to cope with stress.

1.2. Interpersonal relations and impulsivity and anxiety related traits

Consistently, ill mental health is more likely reported by individuals who have experienced more stressful life events (Kessler 1997). Stressful life events include a variety of events, ranging from conflicts with significant other to major financial troubles, accidents and assaults.

The most studied types of conflicts with significant others are adverse relationships between family members and adverse parenting style. This adversity may have an impact on the emergence of mental illnesses and mental health (Rohner et al., 2005). The most important and ubiquitous dimension of parenting, prominent in almost all conceptualizations of parenting and assessments of parenting style over the past 50 years, is parental warmth. Also labeled as acceptance, approving, love, support, positive involvement, closeness, connection etc it refers to the expression of affection, love, appreciation, kindness, and regard; it includes emotional availability, support, and genuine caring (Skinner et al., 2005). Parental affection can be shown physically (e.g., hugging, kissing, caressing, and comforting), verbally (e.g., praising, complimenting, and saying nice things to or about the child), or symbolically in some other way, as with the use of culturally specific gestures (Rohner et al., 2005).

Another imporant construct in parenting research is rejection, also labeled as hostility, disapproval, negativity, aversion, dislike, etc. Expressions of rejection include aversion, hostility, harshness, overreactivity, irritability, and explosiveness; they also include overt communication of negative feelings for the child, such as criticism, derision, and disapproval.

These parenting dimensions are separate, that is, parents who are high on one feature (e.g., warmth) must not necessarily be low on its opposite (i.e., rejection). For example, parents can be low on both of these dimensions, which may reflect low involvement in the parenting role (Skinner et al., 2005). Thus, in order to provide full assessment of family relations, it is equally important to study parental warmth and parental hostility.

One more theme, besides warmth and rejection/hostility in parenting, is control, a construct with much conceptual and empirical confusion. Parental pressure, intrusiveness, and domination assault children's individuality; there is thus a strong rationale for believing that when parents are coercive, they undermine children's psychological development. For example, very high scores in Rohner Parental-Acceptance Rejection Questionnaire control subscale indicate that parents (almost) always try to control the youth's behaviour. If this score is high, parents demand strict, unyielding obedience and total compliance with their directives (Rohner et al., 2005). Still, as developing members of society, children also need to acquire behaviours that are appropriate and acceptable in their cultural contexts, and they require guidance toward such ends. Because parenting that includes firm enforcement, and supervision, is likely to provide children with guidance, it is important to children's development (Grolnick & Pomerantz, 2009). At the most basic level, parents who are able to provide a responsive and warm parenting environment where there are clear expectations for mature behavior can expect to have the most well-adjusted offspring (Holmbeck et al., 1995).

Stressful life events that involve threat, loss, humiliation, or defeat are associated with the onset and course of depression across the life span (Farmer et al, 2001; Kendler et al, 1999). Similarly, families with high rejection or hostility may create vulnerabilities and may exacerbate certain genetically based vulnerabilities, which not only put children at immediate risk for adverse outcomes (such as is the case with abuse), but lay the groundwork for a long-term physical and mental health problems (Repetti et al., 2002). Secondly, when the need for parental warmth is not met, children worldwide – regardless of variations in culture, gender, age, or ethnicity – tend to self-report psychological maladjustment (Rohner et al., 2005).

Positive parenting is also needed to develop self-regulation skills, as according to the neurodevelopmental view on impulsivity, the brain is prepared to be impulsive at birth (Daruna & Barnes, 1993). Indeed, responsive, cognitively stimulating parent-toddler interactions in the 2nd year modestly predicted later cognitive nonimpulsivity and ability to delay gratification (Olson et al., 1990). Corporal punishment, paucity of parental care, high conflict between parents,

and inconsistent discipline was associated with the tendency to act in dysfunctionally impulsive ways in childhood (Eisenberg et al., 2009; Lengua et al., 2010; Olson et al, 2002; Straus & Mouradian, 1998). Although one might expect that in middle adolescence the impact of perceived parental behavior decreases because the importance of relationships with peers and non-parental adults increases (Steinberg & Silk, 2002), there is a line of research that suggest that familial relationships remain salient throughout adolescence. More importantly, such relationships predict the developmental outcomes and psychological adjustment across the life-span (Khaleque & Rohner, 2002). Accordingly, association between parenting and impulsivity is found in many studies from very young age until adolescense (Eisenberg et al., 2009; Lengua et al., 2010; Olson et al, 2002; Peterson & Zill, 1986; Straus & Mouradian, 1998) and adulthood (Kinnally et al, 2009). Similarly to impulsivity, ADHD is a condition sensitive to environmental factors: studies have shown that maltreated children or adolescents with more stressful family environment exhibit significantly more severe symptoms of attention deficit and/or hyperactivity (Famularo et al., 1992; Forssman et al., 2012; Ouyang et al., 2008).

Secondly, adverse environment mediates anxiety-related characteristics. Depression associates with negative relations between mother and child, and with high maternal criticism and high conflict in families independently of whether it was measured with self-report questionnaires or observations of mother-child interactions (Kim Park et al., 2008). Longitudinal data show a significant association between maladaptive parental behaviour and an increased risk of depressive and anxiety disorder, even after controlling for earlier offspring characteristics (i.e., difficult temperament in childhood; Johnson et al., 2001). Although children and adolescents are more depressed if there is a high conflict between parents (Clavarino et al., 2011; El-Sheikh et al., 2012; Peterson & Zill, 1986), or a high level of control characterized by intrusion, and infantilization (Zemore & Rinholm, 1989), adolescent depressive symptomatology does not predict deterioration in family relationships (Sheeber et al., 1997).

It has been found that males are sensitive to the depressogenic effects of interpersonal issues, and noninterpersonal issues like serious difficulties at work, academic performance or income losses (Kendler et al. 2001; Kessler & McLeod, 1984; Shih et al. 2006). Still, girls show greater vulnerability to interpersonal concerns, reactivity to stressful life events involving others, and reliance on support from parents and peers for coping compared with boys (Leadbeater et al., 1999). In addition, although supportive parenting is related to positive outcomes for both boys and girls, the effect is stronger for girls (Craig, 2000; McDermott, et al., 1983; Roche, et al., 2008; Tulviste, 2012).

1.3. Impulsivity and anxiety related behaviours as a result of gene-environment interaction

Thus, growing up in an aversive environment is associated with risky behaviours and disorders, but people show heterogeneity in their response. This heterogenity might depend on gene variants that influence susceptibility to environmental pathogens (Caspi & Moffitt, 2006).

Proportion of genetic effects contributing to aspects of impulsivity – sensation seeking and lack of planning – are around 40–50% (Bezdjian et al., 2011), to ADHD up to 76% (Faraone et al., 2005), to neuroticism around 60% (Rettew et al., 2006), for anxiety disorders 30–40% (Hettema et al., 2001), and adolescent depression from 30% to 50% (Rice, 2009). Although the mode of inheritance of depression, ADHD or personality traits is complex, it has been concluded that multiple genes of modest effect, in interaction with each other and in conjuction with environmental events, produce vulnerability (Geissler & Lesch, 2011; Figure 1). Thus, a single gene-phenotype association is a part of a complex fusion model of a systems neurobiological pathway to behaviour.

Most prominent examples that represent genes encoding key proteins in chemical neurotransmission that are positioned as psychophysiolocal gate-keepers are the serotonin transporter gene (*SLC6A4*), neuronal nitric oxide synthase (NOS1) gene, and α_{2A}-adrenoceptor gene (*ADRA2A*) (Comings et al., 2000; Ebstein 2006; Gerra et al., 2005a; Lesch et al., 1996; Reif et al., 2006; Reif et al., 2009; Uher & McGuffin, 2008; Wakeno et al., 2008).

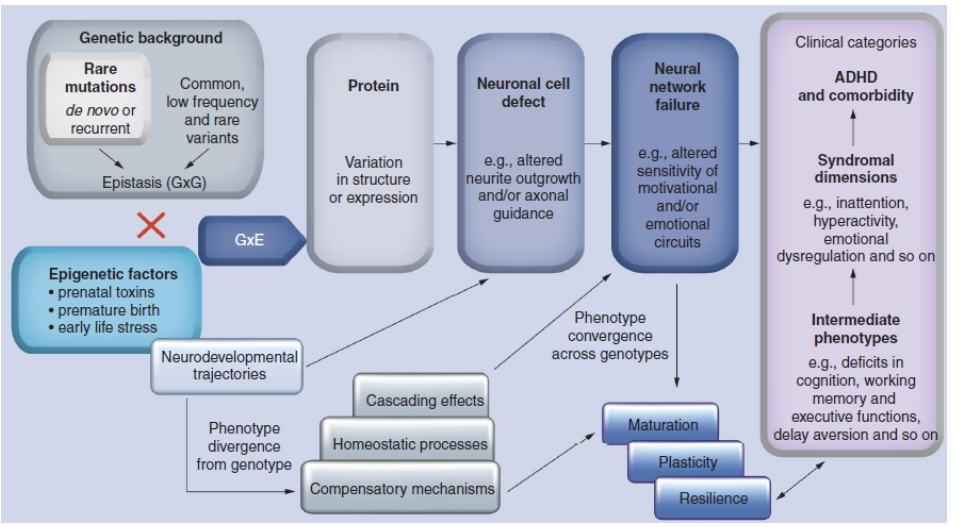

Figure 1. An example of a fusion model of a systems neurobiological pathway to attention-deficit/hyperactivity disorder etiology. The penetrance and phenotypic expression of rare single mutations in a large number of distinct genes is modified by epistatic (i.e., GxG) interaction with a genetic background consisting of common, low-frequency and rare variants. The interaction of genetic variants and epigenetic factors leads to dysfunction of gene products (i.e., proteins), neuronal cell defects and failure of the neural circuit. In addition, GxE interaction influences neurodevelopment trajectories and contributes to the divergence of phenotypes. Environmental factors include prenatal toxin exposure (nicotine, alcohol, illicit drugs and lead), premature birth and early life stress. Genetic variants and epigenetic insults may then influence an organism's resilience, for example, by triggering reactive mechanisms, homeostatic processes and cascading events on neural networks or by impinging on processes dependent on brain maturation and plasticity. Phenotypic convergence arises through overlapping gene defects/epigenetic mechanisms and these secondary pathways. This processural cross-talk ultimately leads to a spectrum of intermediate phenotypes or syndromal dimensions, thus resulting in different categorical diagnoses, one of which is ADHD or associated comorbid disorders. ADHD: Attention-deficit/hyperactivity disorder; GxG: Gene-by-gene; GxE: Gene-by-environment (Geissler & Lesch, 2011).

1.3.1 Serotonin transporter gene linked promoter polymorphism (5-HTTLPR)

Serotonin (5-HT) is a neurotransmitter that is involved in many biological processes, like learning and memory, mood, food intake, sleep, reproduction, circadian rhythm, thermo-regulation, pain perception and social behaviour (Kriegebaum et al., 2010; Lesch, 2007). One key regulator of the serotonin availability is the serotonin transporter (5-HTT), which removes serotonin released into the synaptic cleft. The human 5-HTT is encoded by a gene (*SLC6A4*) in the long arm of chromosome 17, region 1, band 2 (17q12) (Lesch

et al., 1993). The most noted gene polymorphism is named serotonin transporter gene linked polymorphism (5-HTTLPR) locating 1 kb upstream of the 5-HTT gene transcription initiation site, being composed of 16 repeat elements. The polymorphism consists of a 43-base pair (bp) (Wray et al., 2009) insertion or deletion involving repeat elements 6 to 8. The short (s) allele in the 5-HTTLPR is associated with lower 5-HTT function and transcriptional efficiency of the promoter, producing significantly less 5-HTT mRNA and protein, leading to higher concentrations of serotonin in the synaptic cleft compared with the long (l) allele. The s allele appears to have a dominant mode of action (Heils et al., 1996; Lesch et al., 1996), an observation that leads to the grouping of s/s and s/l genotypes in many but not all studies (Caspi et al., 2003; Hariri et al, 2002). However, many studies have also provided support to the additive model, assuming that the risk among subjects with the heterozygous genotype (l/s) is half way between subjects with the homozygous genotypes (Canli et al., 2008; Herman et al., 2003; Neumeister et al., 2002; Schürks et al., 2010).

In the proximity of the Ins/Del locus there are some other polymorphisms. One of them, rs25531, results in an A to G substitution and has been shown to modulate the effect of 5-HTTLPR on transcriptional efficacy. The G allele of rs25531 is in phase with the 5-HTTLPR long allele and mitigates transcriptional efficacy as does the 5-HTTLPR short allele. Therefore, the modulation of 5-HTTLPR by rs25531 results in haplotypes with a high (l_A) or low (l_G, s_A or s_G) transcriptional efficacy (Hu et al., 2006).

An average prevalence of the s/s genotype in populations of Caucasians is 19%, in Asian populations 50–64% and in populations of African descent only 9%. The prevalence of s/l genotype is 48%, 30–39% and 37%, and the prevalence of l/l genotype 33%, 4–12%, and 53%, respectively (Goldman et al., 2010).

Meta-analyses have found an association between 5-HTTLPR s-allele and both NEO neuroticism (Minelli et al., 2011; Sen et al., 2004) and unipolar depression (Clarke et al., 2010). The serotonin transporter gene linked polymorphism is actually one of the few gene variants that has survived as a depression-related genotype the meta-analytic approaches, albeit its effect appears small (Lopez-Leon et al., 2008) – the odds ratio of having depression while carrying the 5-HTTLPR "risk-allele" is very rarely higher than 1.5 (Risch et al., 2009). In some meta-analyses 5-HTTLPR-depression association is not observed. Nevertheless, the s-allele of 5-HTTLPR is consistently related to increased amygdala reactivity to stimuli with negative affective valence (Hariri et al., 2002), that is a frequent finding in major depression (Sheline et al., 2001; Siegle et al., 2007; Suslow et al., 2010).

However, genotypes do not exist in a vacuum; gene expression must depend to some degree on environmental context. Gene-by-environment interactions (G×E) occur when the effect of the environment depends on a person's genotype or, equivalently, when the effect of a person's genotype depends on the environment. For an extreme example, genetic variants influencing tobacco

dependence can have this effect only in environments where exposure to tobacco can occur (Duncan & Keller, 2011). Therefore, inconsistencies in 5-HTTLPR-phenotype association might depend on malleability of the subject carrying a risk-allele by environmental conditions. Since Caspi et al (2003) first showed environmental effect in 5-HTTLPR-depression association – indicating greater environmental sensitivity in s-allele carriers – more than 50 follow-up studies has been conducted. Some studies supported the associations between 5-HTTLPR s-allele and greater stress sensitivity and others did not. These inconsistencies might result from the gender differences in the serotonin system that manifest themselves in functional studies and in a genotype-dependent manner. For example, infusion of the serotonin precursor L-tryptophan increased negative affect in females with the s/s genotype, while in males it increased negative affect only in those with the l/l genotype (Brummett et al., 2008). Next, s-allele might serve as a protective function when 'stress' is not present and this tending might reduce the overall correlation (Homberg & Lesch, 2011). Variability might also depend on quite general and nonspecific measurement of environmental conditions (Monroe & Reid, 2008). For example, studies using objective evidence or detailed interviews to assess environmental adversity consistently found s-allele carriers being more depressed after experiencing adversity from environment, while self-report measures of adversity gave no such result (Uher & McGuffin, 2010). Next, serotonin signalling is strongly associated with social behaviour in mammals (Lesch, 2007) and s-allele carriers show increased trait anxiety due to threat in social evaluation (Crişan et al., 2009), and increased social conformity (Homberg & Lesch, 2011). Therefore, s-allele carriers might be more malleable to interpersonal stressful life events, which might be considered as a separate environmental factor in 5-HTTLPR-depressivity studies.

Thirty years of analyzing genes affecting behaviour in mice, fruit flies, and nematodes have consistently supported the contention that genes influencing behaviour are pleiotropic – that is, they affect more than one trait (Greenspan, 1997). It is also true in humans – several functional candidate genes, including the serotonin transporter gene, are associated with a wide range of psychiatric disorders and/or psychiatrically relevant traits (Kendler & Greenspan, 2006; Ueno, 2003). Thus, 5-HTTLPR s-allele carriers have also higher proneness for substance abuse, self-destructive behaviours (Uher & McGuffin, 2008), and higher prevalence of smoking and illegal drug use in adolescents (Gerra, et al, 2005a,b; Merenäkk et al., 2011). These are behaviours mediated by impulsivity, although no association between 5-HTTLPR and harm avoidance (Minelli, et al., 2011; Sen et al., 2004), attentional, motor and non-planning impulsivity (Lage et al., 2011) is found. However, associations between impulsivity and 5-HTTLPR have not studied in a population representative sample so far. Such an approach would however provide an opportunity to generalise results in a more reliable manner to large populations, as compared with use of conveniece samples.

1.3.2 Nitric oxide synthase and the repeat polymorphism in the promoter region of *NOS1* exon 1f (*NOS1* Ex1f-VNTR)

Serotonergic system is partly regulated by nitric oxide (NO), a gaseous messenger molecule that serves as a modulator of various physiological processes. In peripheral organs, including those of the digestive, respiratory and urogenital tracts, NO performs a neurotransmitter-like role, being released from nitrergic nerves to mediate smooth muscle relaxation. In the central nervous system (CNS), NO is associated with many different behaviours, including learning and memory formation, feeding, sleeping, male and female reproductive behaviour, as well as sensory and motor function (Garthwaite, 2008). NO is produced from the amino acid arginine and the reaction is catalyzed by the enzyme nitric oxide synthase (NOS). One form of this enzyme is the neuronal form (nNOS or NOS1). It is located in nerve cells and inhibits the function of monoamine transporters, which increases the extracellular concentration of monoamine neurotransmitters (Figure 2 (Kiss & Vizi, 2001)).

The human NOS1 gene locates in the long arm of chromosome 12, region 2, band 4, sub-band 3 (12q24.3). This gene comprises 28 coding exons, as well as at least 9 different and alternative first exons (termed exon 1a to 1j), which are spliced to the same second exon. Each of this first exons is driven by its own promoter, however, none of them is translated into protein. The most abundant in the brain are exons 1c and 1f. A repeat polymorphism in the promoter region of *NOS1* exon 1f (*NOS1* Ex1f-VNTR) is highly polymorphic and thus has been dichotomized into long and short alleles. Dichotomization originally was done according to a median split of the repeat number (Reif et al., 2006), with up to 19 repeats being designated as "short". Using a luciferase reporter assay, it was demonstrated that the long (l) variant of *NOS1* Ex1f-VNTR results in significantly increased reporter gene activity as compared with intermediate and short (s) variants (Reif et al., 2009; Rife et al., 2009). In healthy controls, 21% of subjects are homozygous for short alleles, while 28% are homozygous for long alleles (n=8719 subjects). There is no significant difference between samples of different origin, as far as it has been tested (samples from Germany, Italy, Sweden, Estonia, Austria, Norway, and The Netherlands) (Reif, personal communication).

NOS1 ex1f-VNTR short allele is in a gene-dose-dependent fashion associated with impaired functioning of the prefrontal cortex (Reif et al., 2009). Prefrontal cortex has a predominantly inhibitory effect on the amygdala (Gerwitz et al., 1997; Morgan et al., 1993). With regard to the functionality of this connection, lesions to the prefrontal cortex in rats reduce the prefrontal inhibitory action on the amygdala, resulting in an increased difficulty in the extinction of aversive responses (Morgan et al., 1993), as well as impairing the ability to anticipate future negative consequences (Bechara et al., 1996). Studies in mice have revealed similar results – knocking out the *Nos1* results in behavioural changes involving anxiolytic-like phenotype (Zhang et al., 2010)

and increased aggressiveness (Nelson et al., 2006; Trainor et al., 2007). Indeed, homozygosity for short repeats of *NOS1* ex1f-VNTR associates with higher depressiveness (Reif et al., 2006) and with conditions featuring increased impulsivity also in humans: adult ADHD, Cluster B personality disorder, suicidal acts, and violent crime (Reif et al, 2009), but studies with population representative samples are still missing.

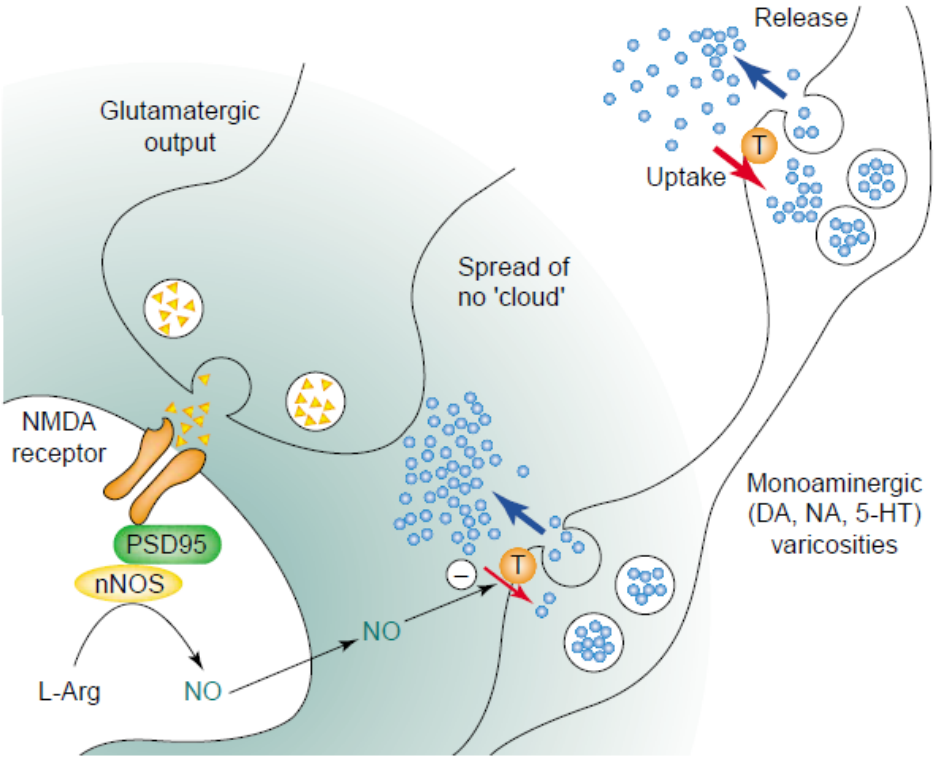

Figure 2. Activation of neuronal nitric oxide synthase (nNOS) in the central nervous system. Release of glutamate stimulates N-Methyl-D-aspartate (NMDA) receptors, and the concomitant influx of Ca^{2+} (not shown) activates nNOS coupled to the receptor via postsynaptic density protein 95 (PSD95). NO synthesized by the enzyme spreads over in a sphere and reaches monoaminergic varicosities in the environment of activated synapses. The actual extracellular concentration of monoamines depends on the balance of release and uptake processes. The appearance of NO, inhibits the function of transporters (T), which increases the extracellular concentration of monoamines in a local volume around the activated glutamatergic synapse, even if the amount of released monoamines is unchanged. Abbreviations: DA, dopamine; NA, noradrenaline (Kiss & Vizi, 2001).

1.3.3. α_{2A}-Adrenoceptors and the *ADRA2A* C-1291G genotype

The noradrenergic projections ascending from the locus coeruleus are acting as a central arousal system, and are implicated in vigilance, memory, irritability, and hostility. There exist two main adrenoceptor subtypes, designated α and β, and further on two α -adrenoceptor subtypes, α_1- and α_2-receptors (Meyer & Quenzer, 2005). Three different subtypes of human α_2-adrenergic receptors have been described: α_{2A}, α_{2B}, and α_{2C}. The α_{2A}-adrenergic receptor is predominant in the frontal cortex of human brain (Grijalba et al., 1996). Activation of presynaptic and somatodendritic α_{2A} adrenoceptors inhibits noradrenaline release and firing of noradrenergic neurons (Starke, 2001). Moreover, the α_{2A}-adrenoceptors modulate release of other major neurotransmitters such as serotonin and dopamine (Scheibner et al., 2001) and α_{2A}-adrenergic receptor activity dependent network involving the prefrontal cortex and locus coeruleus is hypothesised to influence the core pathology of attention deficit/hyperactivity disorder including impulsivity (Arnsten & Li, 2005). The α_{2A}-adrenoceptor gene (*ADRA2A*) is located in chromosome 10q24-26. An MspI restriction site polymorphism (rs1800544) in the promoter region of the gene, originated by a transversion C to G at position −1291, was identified by Lario et al. (1997).

Association studies of this *ADRA2A* MspI polymorphism in families with an ADHD proband using a transmission disequilibrium test analysis have yielded both positive (Park et al., 2005) and negative results (Roman et al., 2003; Wang et al., 2006; Xu et al., 2001). However, previous investigations have demonstrated that the C-1291G polymorphism of *ADRA2A* is associated with the severity of ADHD symptoms in clinical samples. Among ADHD patients, subjects with the GG genotype have more often inattentive and combined symptoms (Roman et al., 2003; Schmitz et al., 2006). Greater improvement of working memory and sustained attention in response to methylphenidate treatment has also been demonstrated in children and adolescents with the G allele than in those without this allele (Cheon et al., 2009; Polanczyk et al., 2007; da Silva et al., 2008). However, even if several *ADRA2A* polymorphisms have repeatedly been associated with hyperactive and inattentive behaviour in psychiatric patients, considerably less is known of attention problems and hyperactivity in population based samples. The above listed evidence gives the reason to suggest the hypothesis that dysfunction of α_{2A}-adrenoceptors may contribute to similar behaviour among healthy individuals. With the exception of the study of Comings et al. (2000) which found the C-1291 G promoter polymorphism in *ADRA2A* associated with indirect hostility, irritability and verbal aggression in students and with impulsivity in normal adults, no study has addressed this question, and none has examined schoolchildren.

Environmental stressors are interacting with biological predisposition: aggressiveness, hyperactivity and inattention might have its origins in genes but are probably influenced by the way these genetic factors interact with and affect an individual's response to the environment. Some trends have been identified in the studies of gene–environment interaction in ADHD: there are gene–

environment interactions, where adverse social factors increase the possibility of expression of risk gene alleles, and other gene-environment interactions where favourable social factors attenuate the genetic risks (Rutter et al., 2006; Sheese et al., 2007). It has recently been demonstrated that maternal criticism and warmth is moderating the effects of genes on ADHD severity (Sonuga-Barke et al., 2008). Adrenergic α_{2A} receptors mediate a number of physiological stress responses, including changes in cognition, cardiovascular function and metabolism (Lafontan & Berlan, 1993). The impact of *ADRA2A* genotype on behaviour may thus depend on early experience of stressful environmental factors like neglect or maltreatment in the family. Thus, we should clarify whether the *ADRA2A* genotype influences symptoms of ADHD in general population, and whether this would depend upon family relations.

2. AIMS OF THE STUDY

Thus, the main aim of this thesis is to study how family relations and/or stressful life events affect associations between some functional gene variants and impulsivity, hyperactivity and anxiety related traits in a population representative sample.

The specific objectives were formulated as follows:

- to study whether impulsivity depends on 5-HTTLPR genotype and whether this association is dependent on environment (**Paper I**);
- to study if interpersonal stressful life events present a different contribution to 5-HTTLPR-depressivity association compared with noninterpersonal stressful life events (**Paper II**);
- to study associations between *NOS1* genotype and impulsivity and *NOS1* genotype and anxiety related phenotypes, and whether any eventual association depends on environmental factors (**Paper III, IV**);
- to study whether the known associations between *ADRA2A* genotype and hyperactive behaviour can be observed in a population-representative sample, and whether these are dependent on environment (**Paper V**).

3. MATERIALS AND METHODS

3.1 Subjects

The sample of this thesis was based on the population representative European Youth Heart Study, originally conducted in Estonia in 1998/1999, which was complemented with a psychology module and subsequently incorporated into the longitudinal Estonian Children Personality, Behaviour and Health Study (ECPBHS). The rationale and procedure of sample formation have been described elsewhere (Harro et al., 2001; 2009). In brief, all schools of Tartu County, Estonia, which agreed to participate (54 of the total of 56) were included into the sampling using the probability proportional to the number of students of the respective age groups in the school, and 25 schools were selected. In 1998/99, all children from grades 3 and 9 were invited to participate and written informed consent was received from 79% of the invited subjects and their parents. The total number of subjects in this sampling was 1176, including 593 in the younger cohort and 583 in the older cohort. The data for the **Paper I** and **II,** were collected during the follow-ups of younger cohort in 2004 and the data for **Paper III** and **IV** were collected during the follow-ups of younger cohort in 2004 and 2007. We were able to recruit, respectively, 81% (n= 483; 222 males and 261 females; mean age 15.3±0.3 years) and 76% (n= 453; 201 males and 252 females; mean age 18.0±0.3 years) of the original younger cohort. Adolescents and their parents gave their informed consent in all study waves. The data for the **Paper V** was collected during the second follow-up of the older cohort which was conducted in 2008, when the participants were approximately 25 years old (n=541; 230 male and 311 female) (Tomson et al., 2011). All participants were Caucasians. Permission for the studies was obtained from the Committee of Ethics of the University of Tartu, Estonia.

3.2. Measurements

3.2.1. Family relations

3.2.1.1. Tartu Family Relationships Scale (Papers I, II, III, IV)

Tartu Family Relationships Scale is a child-report scale, that assesses relationships in the family and was composed for Estonian Children Personality, Behaviour and Health Study. Forty nine relevant items were included in factor analysis. Principal component analysis was computed on a different sample of 885 adolescents (43% boys and 57% girls) with mean age 16.1 years (SD=1.56 years). As a result, four subscales were extracted using the Cattell criterion (Cattell, 1966) and were named Closeness (15 items, e.g., "Our family is dedicated to each other", "The marriage of my parents is happy"), Support (7 items, e.g., "My family supports me", "Someone in the family helps (has helped) me to feel myself important and special"), Misprize (10 items, e.g., "I

can make no decision on my own", "I am depreciated at home"), and Abuse (emotional and physical, 7 items, e.g., "Were you ever hit by someone in your family or have you experienced physical violence in your family?"). Items were presented in terms of 4 or 5-point Likert scale. More information about the subscales is presented in Table 1. Basing on the similarity in the results, the subscales of Closeness and Support were added together under a common name "Warmth in the family" and the subscales of Abuse and Misprize were added together under a common name "Maltreatment" in **Paper I, II, and IV**.

Table 1. The description and results of the factor analysis of the subscales of the Tartu Family Relationships Scale based on the data from the first follow-up of the younger sample and the original study of the older sample.

Subscale	Number of items	Cron-bach's α	Inter-item correlation	Factor loadings	Eigen-value	Explained variance
Warmth						
Closeness	15	0.94	0.52	0.45–0.82	13.86	75%
Support	7	0.80	0.37	0.44–0.65	1.54	41%
Maltreatment						
Misprize	10	0.86	0.40	0.45–0.77	3.43	53%
Abuse	7	0.83	0.42	0.52–0.75	1.93	39%

3.2.1.2. Parental Acceptance-Rejection/Control Questionnaire (PARQ/Control) (Paper III)

Child-report Parental Acceptance–Rejection/Control Questionnaire: Mother (Short Form) (Rohner, 2005) is a 29-item self-report measure assessing youth perceptions of:

- maternal warmth/affection (verbal (praise, compliment, say nice things to or about, etc) or physical (kiss, hug, fondle etc)),
- hostility/aggression (verbal (curse, sarcasm, belittling, say thoughtless, unkind, cruel things to or about, etc) or physical (hit, bite, scratch, shove, pinch, etc)),
- indifference/neglect (physical and psychological unavailability of parent, pays no attention to needs of child, etc),
- undifferentiated rejection (beliefs that their parents do not really love, want, appreciate, or care about the child)
- behavioural control (permissiveness–strictness).

Respondents filled out the Estonian-language version of this instrument (Tulviste & Rohner, 2010) on a 4-point Likert-like scale from 1 (almost always true) to 4 (almost never true). To facilitate the interpretation of the results the

scales were reversed so that that the higher score represented more adversity from mother. The total score of the PARQ/Control was obtained with summing reversed warmth scale and hostility/aggression, indifference/neglect and undifferentiated rejection scale. The Cronbach α's of the PARQ/Control subscales in our sample were good, rangeing 0.77 to 0.87 except the Control subscale with Cronbach α 0.59.

The correlations between Tartu Family Relationships Scale and PARQ/Control Questionnaire are presented in Table 2.

Table 2. Intercorrelations (Spearman r) between the subscales of Tartu Family Relationships Scale and PARQ/Control (correlations $p<0.05$ are presented in bold).

	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)	(10)	(11)
Tartu Family Relationships Scale											
Closeness (1)											
Support (2)	**0.73**										
Warmth (3)	**0.97**	**0.86**									
Misprize (4)	**–0.54**	**–0.54**	**–0.58**								
Abuse (5)	**–0.55**	**–0.45**	**–0.54**	**0.49**							
Maltreatment (6)	**–0.63**	**–0.58**	**–0.66**	**0.88**	**0.83**						
PARQ											
Warmth (7)	**0.49**	**0.65**	**0.58**	**–0.50**	**–0.40**	**–0.52**					
Hostility (8)	**–0.22**	**–0.24**	**–0.25**	**0.45**	**0.40**	**0.49**	**–0.42**				
Indifference (9)	**–0.43**	**–0.48**	**–0.47**	**0.49**	**0.43**	**0.54**	**–0.66**	**0.48**			
Undifferentiated rejection (10)	**–0.32**	**–0.34**	**–0.36**	**0.45**	**0.38**	**0.46**	**–0.46**	**0.55**	**0.52**		
Total score (11)	**–0.51**	**–0.61**	**–0.58**	**0.59**	**0.49**	**0.63**	**–0.91**	**0.62**	**0.86**	**0.63**	
Control	–0.05	–0.00	–0.04	**0.35**	**0.24**	**0.33**	–0.05	**0.39**	**0.19**	**0.26**	**0.19**

3.2.2. Stressful life events (Papers II and IV)

Two somewhat different scales of stressful life events were used in **Paper II** and **Paper IV**. Stressful life events in preceding year were assessed in **Paper II.** In **Paper IV**, the scale was constructed from the existing items in the socio-economic questionnaire after conducting the data collection, and stressful life events during the life course were assessed.

Paper II: the list of stressful life events consisted 17 adverse life events involving divorce, including termination of any romantic relationship, separation from a significant other, conflicts with husband or wife or partner,

conflicts with significant other / family member, personal crisis, death or serious illness of significant other / family member, having been assaulted, major financial trouble, difficulties with residence, serious illness or injury, laying off or sacked from work, trouble with the law, having been robbed, serious problems at work, traffic accident, other accident considered serious. The history of stressful life events in a preceding year was self-reported. The events were recorded as dichotomous variables (present or not present) and were then counted to form the number of experienced stressful life events.

Stressful life events were classified as those with involvement of significant others and/or family members vs being primarily noninterpersonal (Table 3). We then classified the subjects into groups with low and high level of exposure to stressful life events (0–3 vs ≥4 events), interpersonal stressful life events and noninterpersonal stressful life events (both 0–1 vs ≥2 events). Such classification placed approximately two thirds of participants into the low exposure groups and one third into the high exposure groups.

Table 3. Classification of stressful life events into interpersonal and noninterpersonal.

Interpersonal stressful life events	**Noninterpersonal stressful life events**
Divorce, including termination of any romantic relationship	Having been assaulted
Separation from a significant other	Major financial trouble
Conflicts with spouse or partner	Difficulties with residence
Conflicts with significant other / family member	Serious illness or injury
Personal crisis of significant other / family member	Laid off or sacked from work
Death of significant other / family member	Trouble with the law
Serious illness of significant other / family member	Having been robbed
	Serious problems at work
	Traffic accident
	Other accident considered serious

Paper IV: the list of stressful life events consisted of 15 adverse experiences including parental death and divorce/separation, unemployed parent, parental alcoholism, poverty, poor living conditions, poor health, accidents and traumas, physical abuse, emotional abuse, severe burden/serious concerns, suicidal attempts, leaving home for several days without telling anyone, depression of a close relative, committed suicide, or suicide attempt of a close relative.

The events were recorded as dichotomous variables (present or not present) and were then counted to form the number of experienced adverse life events. On the basis of the percentile distribution (25–50–25), the subjects were divided to form groups with no history of stressful life events, 1–2 stressful life events and three and more life events.

3.2.3. Impulsivity

3.2.3.1. Adaptive and Maladaptive Impulsivity Scale (AMIS; Papers I and III)

The scale is a short instrument consisting of four subscales. Two of them are based on the Dickman Impulsivity Inventory (Dickman 1990), measuring functional (named "Fast Decision Making" in AMIS) and dysfunctional impulsivity (named "Thoughtlessness" in AMIS) and two base on impulsivity related subscales of NEO-PI (Neuroticism Extraversion Openness Personality Inventory, Costa & McCrae 1989, adapted into Estonian by Pulver et al., 1995): Impulse Control (named "Disinhibition") subscale under the domain of Neuroticism and Excitement Seeking (named "Excitement Seeking") subscale under the domain of Extraversion. Two of the four subscales of AMIS, Thoughtlessness and Disinhibition, measure the maladaptive types of impulsivity and the other two, Fast Decision-Making and Excitement Seeking, measure the adaptive types of impulsivity.

3.2.3.2. Barratt Impulsiveness Scale (BIS-11; Papers I and III)

Barratt Impulsiveness Scale (BIS-11) (Patton et al., 1995) was used for measuring impulsiveness. The Estonian version of the scale was adapted on 683 subjects with mean age 19±8 years of age ranging from 14–66. Twenty seven out of the original 31 items formed a single scale with average inter-item correlation r=0.13 and inner reliability expressed as Cronbach Alpha 0.80 (Paaver et al., 2007).

3.2.4. Symptoms of attention-deficit/hyperactivity disorder (Paper V)

3.2.4.1. Hyperactivity Scale

Ratings on aggressiveness, motor restlessness, and concentration difficulties were obtained from the class teachers who had known the child for at least three years, using the 7-point Hyperactivity Scale of af Klinteberg (1988). The original study using this instrument in its

Swedish version in a longitudinal design conservatively estimated the test–retest reliability for the rating variables at 0.80 (af Klinteberg, 1988; Magnusson et al., 1975). The teachers were instructed to use the boys and girls in their own class as reference groups. Hyperactivity score was calculated after af Klinteberg

and Oreland (1995) by summing the scores of Motor Restlessness and Concentration Difficulties. Data of aggressiveness, motor restlessness and concentration difficulties were available for 402 adolescents.

3.2.4.2. Swanson, Nolan and Pelham Questionnaire IV (SNAP-IV)

The teacher-report version of the SNAP-IV (Swanson et al., 2001) was also used to assess symptoms of ADHD in adolescents. Each of the 18 items of the SNAP-IV provides a word-to-word description of a symptom of DSM-IV ADHD (American Psychiatric Association, 1994), and instructs the rater to indicate whether the child exhibits the symptom "not at all", "just a little", "pretty much", or "very much". The scores of SNAP-IV can be divided into Inattention and Hyperactivity/Impulsivity subscales. SNAP-IV scores were available for 429 adolescents.

3.2.5. Neuroticism and extraversion (Paper IV)

The five-factor personality (Neuroticism, Extraversion, Openness to Experience, Agreeableness, and Conscientiousness) assessment was carried out at age 15 with a 240-item questionnaire Estonian Personality Item Pool NEO (EPIP-NEO) (Mõttus et al., 2006) and at age 18 with a 60-item inventory "Short Five" (S5). Both questionnaires measure the five-factor construct with adequate reliability and are highly intercorrelated (Konstabel et al., 2012). Data about personality at ages 15 and 18 were available for 468 and 452 participants, respectively.

3.2.6. Anxiety (Paper IV)

Spielberger State-Trait Anxiety Inventory (Spielberger, 1983) was used at age 18. The State scale of Spielberger State-Trait Anxiety Inventory was used at age 15. Data were available for 447 (State Anxiety), 441 (Trait Anxiety) at age 18, and for 450 participants at age 15

3.2.7. Montgomery-Åsberg Depression Rating Scale (Paper II and Paper IV)

Depressiveness was measured by Montgomery-Åsberg Depression Rating Scale self-assessment version (Montgomery & Åsberg, 1979). Data were available for 535 in **Paper II and** for 440 participants in **Paper IV**.

3.2.8. Genotyping

3.2.8.1. 5-HTTLPR

The alleles at the 5-HTTLPR locus were amplified from genomic DNA using polymerase chain reaction (PCR) as previously described (Paaver et al., 2007). The polymorphic region was amplified using the primers 5-HTTLPR-F: CAA CCT CCC AGC AAC TCC CTG TA, 5-HTTLPR-R: GAG GGA CTG AGC TGG ACA ACC AC, where the forward primer was fluorescently labeled with a 5′-FAM. Reagents and conditions for the PCR were: 1×PCR buffer (Perkin Elmer, AmpliTaq Gold buffer II), 200 μM dNTP with 50% of dGTP replaced with 7-deaza-dGTP, 2mM $MgCl_2$,1 μM of each primer, 1 U Taq polymerase (Perkin Elmer, AmpliTaq Gold), and 20 ng genomic DNA, in a total reaction volume of 10 μL. The reaction started with 10 min at 95 °C, followed by 40 cycles with 30 s at 95 °C, 30 s at 59 °C, 30 s at 72 °C, and ended with 7 min at 72 °C. PCR products were then run on an ABI PRISM 3700 DNA analyzer (Applied Biosystems, USA), and scored using the software GeneMarker 1.5 (SoftGenetics, USA). All genotypes were manually checked on chromatograms to detect inconsistencies, and where needed, amplified and scored a second time. 5-HTTLPR genotype was assessed in 435 children and 191 (44%) of subjects were homozygous for l allele, 189 (43%) were heterozygous and 55 (13%) were homozygous for the s allele. Genotype frequencies were in Hardy–Weinberg equilibrium.

For triallelic classification we used the method by Anchordoquy et al. (2003), with minor modifications (Tomson et al., 2011). Genotype frequencies were in Hardy–Weinberg equilibrium.

Tri-allelic genotypes were transformed into a bi-allelic model according to their level of expression as follows: lG/lG, lG/s, and s/s were designated as s's', lA/s and lA/lG as l's', and lA/lA as l'l'. Triallelic classification of genotype frequencies separately in males and females is presented in Table 4. Data of 5-HTTLPR genotype were available for 540 subjects.

Table 4. Triallelic classification of 5-HTTLPR genotypes in the study participants in Paper V.

	l'l' genotype	**l's' genotype**		**s's' genotype**			**Total**
	l_A/l_A	**l_A/s**	**l_A/l_G**	**l_G/s**	**s/s**	**l_G/l_G**	
Females	97 (31%)	121 (39%)	23 (7%)	19 (6%)	50 (16%)	1 (1%)	311 (100%)
Males	74 (32%)	85 (37%)	21 (9%)	14 (6%)	33 (15%)	2 (1%)	229 (100%)
Total	171 (32%)	206 (38%)	44 (8%)	33 (6%)	83 (15%)	3 (1%)	540 (100%)

3.2.8.2. NOS1 ex1f-VNTR

NOS1 ex1f-VNTR has been analyzed as published previously (Reif et al., 2009). One of the primers was labeled with a fluorescent dye (cy-5; TIB MolBiol, Berlin) enabling detection of the polymerase chain reaction product. Electrophoretic separation of the PCR products was performed using a CEQ8000 DNA-sequencer (Beckman-Coulter, Krefeld, Germany). *NOS1* ex1f-VNTR alleles were grouped as short (180–196 repeats, s) and long alleles (198–210 repeats, l). For the mixed-effect analysis of variance, that incorporated data from two follow-up studies – 2004 and 2007 –, data of *NOS1* exlf VNTR genotype were available for 524 participants. In interaction analysis data from follow-up 2007 were used: data of *NOS1* exlf VNTR genotype were available for 435 participants (Table 5). Quality control comprised genotyping of two constant external controls every 90 samples, as well as genotyping 2% of all samples (randomly) twice. Concordance rates were 100%. The sample has been genotyped in one batch, call rate was 91%. Dropouts were due to missing amplicons, repetition of genotyping dropouts did not result in recovery of genotypes so that we assume that dropout most likely is due to DNA degradation. Genotypes were in Hardy-Weinberg equilibrium.

Table 5. *NOS1* exlf-VNTR genotypes in the participants of follow-up in 2007 (Papers III and IV).

	l/l	**s/l**	**s/s**	**Total**
Males	52 (26%)	113 (57%)	34 (17%)	199 (100%)
Females	63 (27%)	111 (47%)	62 (26%)	236 (100%)
Total	115 (26%)	224 (52%)	96 (22%)	435 (100%)

3.2.8.3. ADRA2A

The MspI polymorphism (rs1800544) in the promoter region of the ADRA2A gene was amplified by the PCR (Lario et al., 1997) using the primers and protocols previously reported (Mäestu et al., 2008). The forward primer was 5′-TCA CAC CGG AGG TTA-3′ and the reverse primer was 5′-TCC GAC GAC AGC GCG-3. If there was any doubt in determination the genotype correctly, the assay was run again. Genotypes were in Hardy–Weinberg equilibrium.

4. RESULTS AND DISCUSSION

4.1. 5-HTTLPR in environment-phenotype association

4.1.1. 5-HTTLPR, family relations and impulsivity (Paper I)

Serotonin system has been shown to be associated with impulsivity (Evenden, 1999). A variance in the key gene in the serotonin system, the serotonin transporter linked gene polymorphism 5-HTTLPR, is associated with impulsive behaviour (Gerra et al., 2005a; Li & He, 2007). Still, 5-HTTLPR-impulsivity association has not been studied in a population representative sample. As environment is an important mediator in 5-HTTLPR- behaviour association (Caspi et al., 2003) and aversive relations in the family are associated with the development of child's impulsivity (Olson et al., 1990; Straus & Mouradian, 1998), family relations were analysed in interaction with 5-HTTLPR.

We found the s-allele carriers having higher disinhibition compared to l/l homozygotes, especially in boys. This is in accordance with earlier studies indicating higher prevalence of s-alleles in subjects with more impulsive behaviour (Li & He, 2007) and studies indicating s-allele carriers having higher scores in anxiety related traits (Clarke et al., 2010; Minelli et al., 2011; Sen et al., 2004), that correlate positively with higher dysfunctional impulsivity (d'Acremont & Linden, 2007; Granö et al., 2007; Hutchinson et al., 1998).

We also found a G x E interaction effect, indicating that low warmth in the families of the s-allele carrying girls is associated with higher thoughtlessness, disinhibition and impulsivity according to BIS-11 (Figure 3). In boys, the adaptive types of impulsiveness were associated with positive relations in the family and boys with high warmth in the family and l/l genotype had lower maladaptive impulsivity than s-allele carriers. Thus, girls seems to have worse outcome from dysfunctions in the family, while boys gain more from positive parenting.

Gender differences are in accordance with earlier studies demonstrating that 5-HTTLPR s-allele and adverse environment interaction is stronger in female subjects, expressing in higher vulnerability to depression and lower agreeableness only in s-allele carrying women (Eley et al., 2004; Grabe et al., 2005; Lesch & Merschdorf, 2000; Sjöberg et al., 2006). In addition, in genetics of personality, several studies have shown that the path from gene to behaviour may be different in males and females as sexual differences start out developmentally as differences in gene expression in the sex determination pathway. In addition, evidence on psychiatric, including substance use disorders in human populations and a range of behavioural phenotypes in simpler animals suggest that modification of genetic effects by sex is probably a common phenomenon (Kendler & Greenspan, 2006).

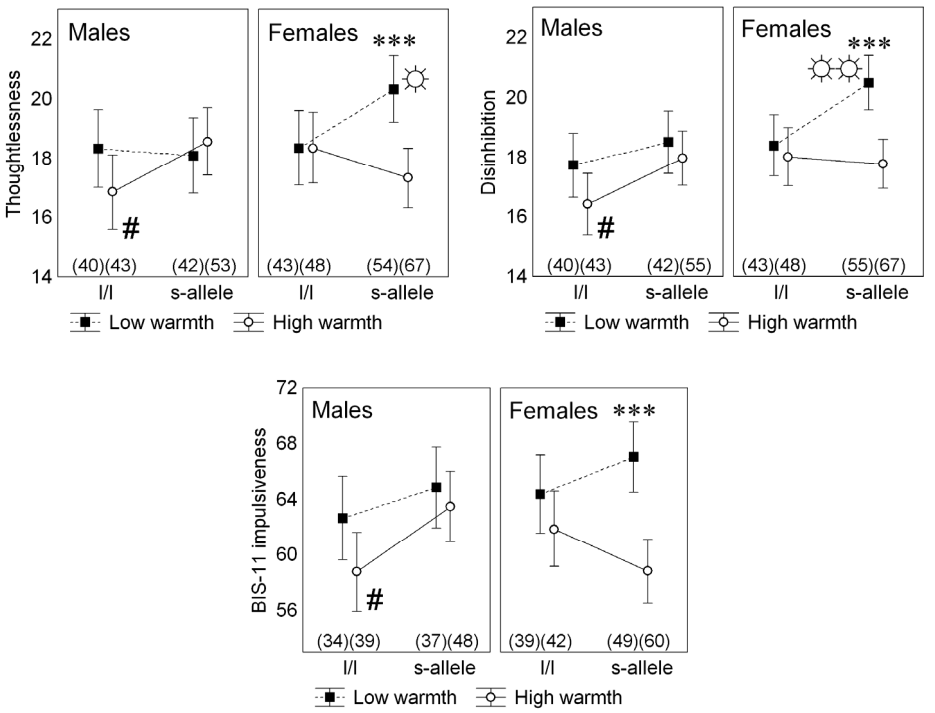

Figure 3. 5-HTTLPR × environment × gender interaction effect on depressiveness. *** $p<0.001$, different from same gender adolescents with corresponding allele and higher warmth in the family; # $p<0.05$ different from same gender adolescents with s-allele and high warmth in the family; ☼☼ $p<0.01$, ☼ $p<0.05$ different from same gender adolescents with the l/l genotype and low warmth in the family. The number of subjects in each group in brackets. Whiskers indicate 95% confidence intervals.

The impact of 5-HTTLPR s-allele and adverse family relations on impulsivity is suggested to be developmental rather than immediate, as serotonin plays an important role in brain development (Lesch & Gutknecht, 2005). According to the neurodevelopmental view on impulsivity, the brain is actually prepared to be impulsive at birth, and the self-regulation skills are the product of learning and positive parenting. Thus, harsh treatment, as well as neglect by parents, may both result in the inability to regulate emotions and impulses in child (Daruna & Barnes, 1993). Although the impact of adverse family environment may have been stronger in earlier age, the post-natal development of prefrontal cortex, which is potentially important structures in impulse and emotion regulation (Kim & Lee, 2011), continues through adolescence until adulthood (Nelson, 2006).

4.1.2. Different stressful life events in 5-HTTLPR – depressivity association (Paper II)

Besides impulsivity, 5-HTTLPR is associated with anxiety related traits and depression (Lesch et al., 1996; Lopez-Leon et al., 2008). The association between 5-HTTLPR and depression has been in the highlight of studies for more than a decade now. Starting from Caspi et al (2003), a huge number of 5-HTTLPR x E interaction studies on depression has been conducted, but with variable outcome. This might result from an unconventional and inconsistent approach in assessing life stress (Monroe & Reid, 2008), that is common in G × E studies and influences outcomes in 5-HTTLPR x environment interaction effect on depressivity (Uher & McGuffin, 2010; Karg et al., 2011). Environmental adversity may include issues in social behaviour, that is known to be strongly associated with serotonergic signalling in mammals (Lesch, 2007). For example, increased trait anxiety due to threat in social evaluation or in interpersonal situations has been found in 5-HTTLPR s-allele carriers (Crişan et al., 2009), and the s-allele carriers also show increased social conformity (Homberg & Lesch, 2011). Thus, interpersonal stressful life events might be considered as a separate environmental factor in 5-HTTLPR-depressivity studies.

Indeed, we found, that the 5-HTTLPR × gender interaction effect on depressiveness depended on experience of interpersonal stressful life events, and it did not depend on noninterpersonal stressful life events. In females, s'-allele carriers had lower depressiveness if they had experienced a smaller number of interpersonal stressful life events recently, but noninterpersonal stressful life events had no significant genotype-dependent effect on female depressiveness. This result is in principle consistent to the meta-analysis by Karg et al., (2011), who found subjects with the s-allele being very sensitive to maltreatment in childhood, that includes the most severe interpersonal stressful life events such as neglect from parents, physical or sexual abuse, or being bullied. Therefore, the s-allele carriers might be more sensitive to interpersonal stressful life events. Our results also suggest them being more capable of gaining from positive interpersonal relationships that is similar to another recent study where children with the s/s genotype were more likely to respond to psychotherapy (Eley et al., 2012). It is also found, that s-allele carriers show increased social conformity, outperform subjects carrying l-allele in an array of cognitive tasks (Homberg & Lesch, 2011), have less concentration difficulties and inattention symptoms and subjects with s/s genotype have higher likelihood to obtain higher education level (Kiive & Harro, 2012), that might reduce a risk for exposure to further adverse life events, and for subsequent development of depression. Thus, these results support the notion that "vulnerability genes" or "risk alleles" might, at times, be more appropriately conceptualized as "plasticity genes" or "malleability genes", because they seem to make individuals more susceptible to environmental influences – for better and for

worse (Belsky et al., 2009). Thus, optimal functioning of social network is very important for females with the s'-allele (Figure 4B), and lack of issues with and the wellbeing of their important others is strongly associated with their mental health.

Within the same birth cohort, we found male participants with the l'/l' genotype being malleable to both kinds of environmental stress (Figure 4). Thus, while in females the genotype effect on depressivity depended on issues with important others, males with l'/l' genotype were rather affected by both type of stressors. This is consistent with previous findings that females are mainly sensitivite to interpersonal issues and males are vulnerable to the depressogenic effects of both interpersonal issues and noninterpersonal difficulties (Kendler et al., 2001; Kessler et al., 1984; Shih et al., 2006). In a number of previous studies the increased effect of environmental adversity in s-allele carriers has not been found in males while present in females (Eley et al., 2004; Grabe et al., 2005; Hammen et al., 2010). Instead, males with the l'/l' genotype were more sensitive to adverse life events, as a number of previous studies have already found (Brummett et al., 2008; Sjöberg et al., 2006; Surtees et al., 2006). These differences between genders might appear for the reason that there are functional differences in the serotonin system in males and females that have implications for emotional wellbeing, and are 5-HTTLPR-dependent. For example, infusion of the serotonin precursor L-tryptophan increases negative affect in females with s/s genotype, while in males it increased negative affect only in those with l/l genotype (Brummett et al., 2008).

Although there were differences in measuring the environment and phenotypes in **Paper I** and **Paper II**, it is possible to observe some similarities in the results of these studies. In both **Papers** females were vulnerable to environment if they had s or s'-allele, compared to females with l/l or l´/l´genotypes, respectively. In addition, they were vulnerable to similar environmental conditions. Both in **Paper I** and **Paper II** females were sensitive to stressful environment associated with important others: females with s-allele were sensitive to the lack of warmth in the family in **Paper I** and s'-allele females were vulnerable to the lack of issues with important others in **Paper II**. Still, although lack of warmth increased the maladaptive impulsivity in s-allele females, lack of interpersonal problems decreased the depressiveness of s'-allele females. Thus, s-allele might indicate malleability in females. Therefore, the higher maladaptivive impulsivity in an adverse environment might be compensated with lower depressivity in a supportive environment. Males with l/l genotype had lower maladaptive impulsivity in families with high warmth and males with l'/l' genotype had lower depressivity if they had experienced less stressful life events recently. Thus, 5-HTTLPR x E interaction effect might not depend simply on gender as found previously in many studies, but also on measurement of the environment, more specifically, on issues with significant others.

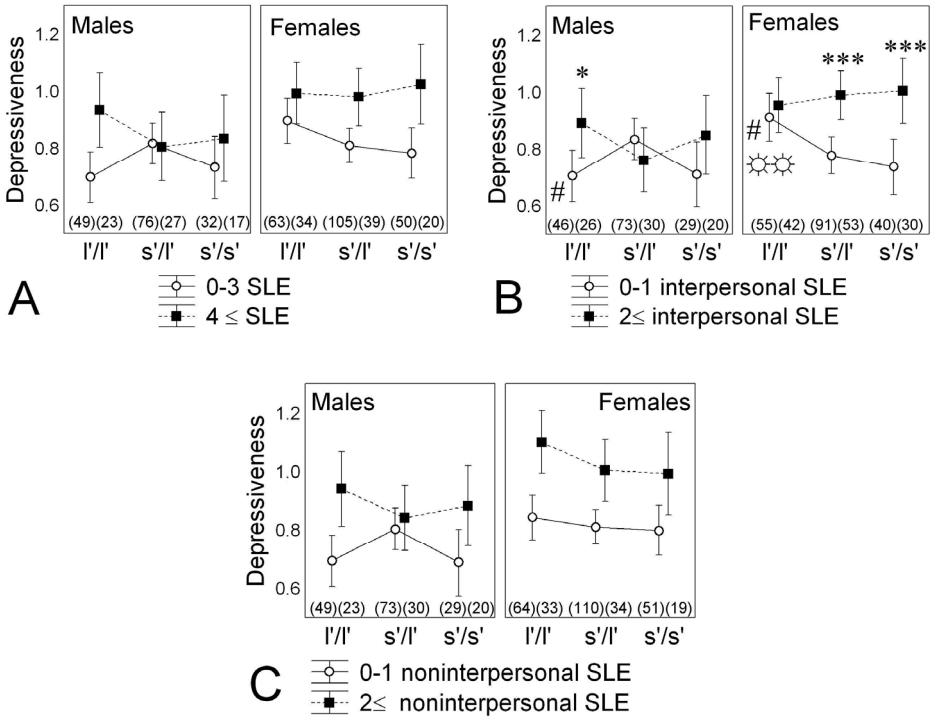

Figure 4. 5-HTTLPR × environment × gender interaction effect on depressiveness. SLE –stressful life events. *** $p<0.001$, * $p<0.05$ different from same gender adolescents with corresponding genotype and lower exposure to SLE; # $p<0.05$ different from same gender adolescents with the s'/l' genotype and lower exposure to SLE; ☼☼ $p<0.01$ different from same gender adolescents with the s'/s' genotype and lower exposure to SLE. The number of subjects in each group in brackets. Whiskers indicate 95% confidence intervals. Depressiveness is presented on a logarithmic scale.

4.2 NOS1 ex1f-VNTR in environment-phenotype association (Paper III and Paper IV)

Beyond the serotonergic system, there are only a few key molecules which are consistently found to be linked to impulsive behaviours. Among those, nitric oxide synthase 1 (NOS1) is of special interest, as it is tightly linked to the serotonergic system (Kiss & Vizi, 2001). Homozygosity for short repeats in the promoter region of the alternative first exon 1f of human gene encoding NOS1 goes along with conditions featuring increased impulsivity: adult ADHD, cluster B personality disorder, suicidal acts, violent crime (Reif et al., 2009), and higher depressiveness in psychiatric patients (Reif et al., 2006). Association between *NOS1* ex1f-VNTR and impulsivity or anxiety related traits in a population representative sample is still unknown. In addition, studies have not

indicated if and how environment mediates *NOS1* ex1f-VNTR -phenotype association.

Our studies showed that s-allele carriers scored high on neuroticism and state anxiety. Although aspects of impulsivity are included in neuroticism in the five-factor model of personality, impulsivity did not explain the genotype effect on neuroticism (**Paper IV**). Higher neuroticism and state anxiety lead to higher sensitivity toward life events (Homberg & Lesch, 2011). Therefore, people with *NOS1* s-alleles should be more sensitive to adversities in the environment. Accordingly, participants with the s/s genotype were found to describe themselves as more thoughtless and disinhibited persons, if having unfavourable relations in their family (**Paper III**) (Figure 5). The result of the s-allele carriers being more vulnerable to adverse environment was found again in the **Paper IV**, as adolescents carrying the s-allele had high state anxiety if having been subjected to adverse environment.

In males, *NOS1* ex1f-VNTR genotype is associated with extraversion and adaptive impulsivity (**Paper IV** and **III**, respectively). These two constructs are similar, as both include components that reflect dominance or even overt agressiveness, such as activity and assertiveness. Analysis of covariance indeed suggested that association of the *NOS1* genotype with extraversion is related to its effect on adaptive impulsivity (**Paper IV**). Comparable results have been found in mouse studies: male mice lacking the *Nos1* gene display more agression-like behaviour – that includes high locomotor activity, similar to extraversion and impulsivity in humans – while there was no such difference in female mice (Nelson et al., 2006). Extraversion is negatively associated with depressiveness (Chioqueta & Stiles, 2005), and therefore, the s-allele leading males towards being more active and extraverted may prevent them being increasingly depressed in adversity. That might be an explanation why adverse environmental conditions affected only males with the l/l genotype (**Paper IV;** Figure 6A & Figure 6C) .

One can only speculate how such a balanced selection effect might make sense: under positive conditions, male s-allele carriers feature the advantageous genotype in that they display by increased adaptive impulsivity (**Paper III**) and extraversion (**Paper IV**). In the presence of life adversity, s/s carriers have to pay the price in featuring higher maladaptive impulsivity (**Paper III**) and an accordingly increased risk for related psychopathology. On the contrary, male l/l participants have lower impulsivity (**Paper III**) and extraversion (**Paper IV**) that could be led to higher malleability by adverse environment. Female s-allele carriers present higher scores in anxiety related traits (**Paper IV**; Figure 6). This supports the notion that adverse life events interact with the risk allele to increase impulsivity in males and neuroticism / depressiveness in females, i.e., the preponderant sex-specific sequelae of life adversity: while males may be imprisoned, females seek treatment. Thus, adverse environment leads to different psychological outcomes in males and females dependent on *NOS1* genotype.

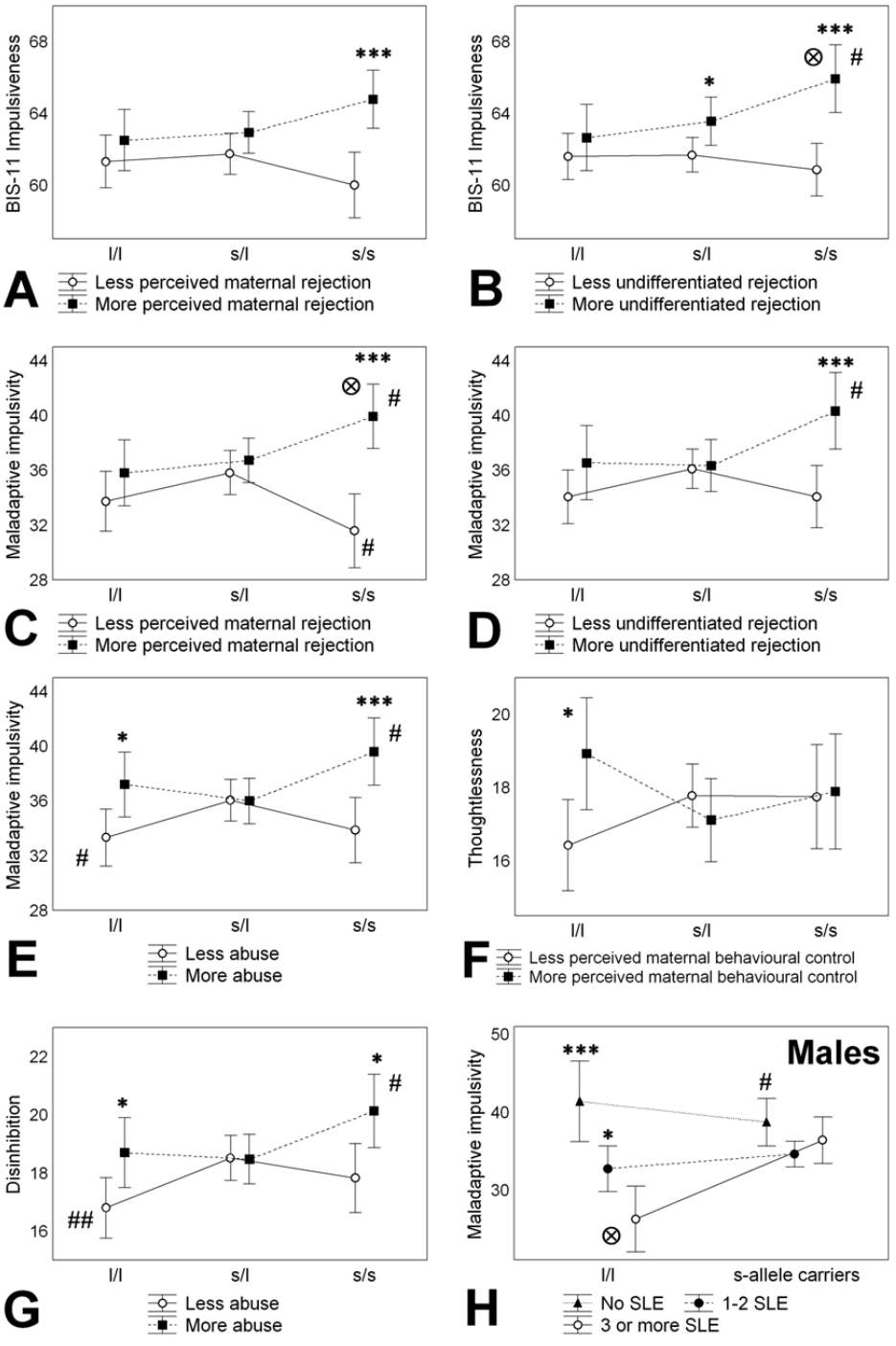

Figure 5. a–g The interaction effects of NOS genotype and family relations on different types of impulsivity. **h** The interaction effect of NOS genotype and stressful life events on maladaptive impulsivity in males. **a-g** ***p<0.001, *p<0.05 different from adolescents with less adversity or less control in the family; $^{\#\#}$p<0.01, $^{\#}$p<0.05 different from adolescents with similar family relations and s/l genotype; $^{\otimes}$p<0.05 different from adolescents with similar family relations and l/l genotype. **h** ***p<0.001, *p<0.05 different from males with l/l genotype and 3 or more SLE; $^{\#}$p<0.05 different from males with s-alllele and 1–2 SLE; $^{\otimes}$p<0.05 different from adolescents with s-allele and 3 or more SLE

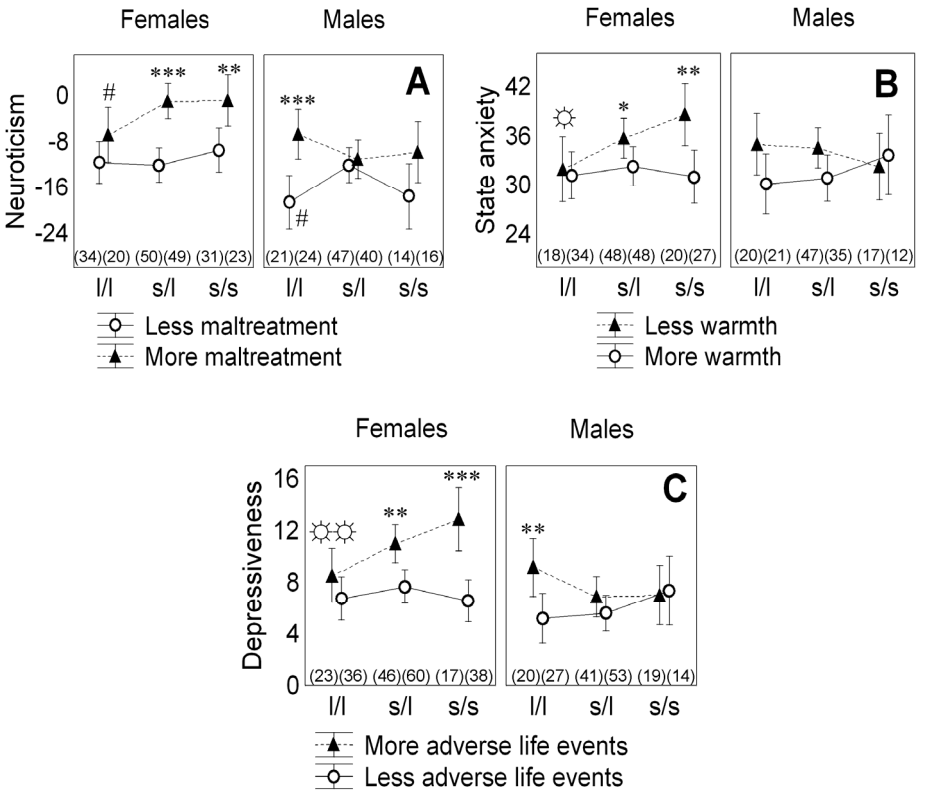

Figure 6. Gene × environment interaction effects on neuroticism, anxiety and depressiveness in males and females. The number of participants in each group is presented in brackets. Whiskers indicate 95% confidence intervals. *** p<0.001, ** p<0.01 different from adolescents with the same genotype, same sex and better environmental conditions; # p<0.05 different from adolescents with similar environmental conditions, same sex, and s/l genotype; ☼☼ p<0.01, ☼ p<0.05 different from adolescents with similar environmental conditions, same sex, and s/s genotype.

4.3 ADRA2A in environment-hyperactivity association (Paper V)

There is a strong evidence that adequate noradrenergic function is required for optimal function of the prefrontal cortex, which is important for attention control (Arnsten, 1999; Arnsten & Li, 2005). Noradrenaline release and firing of noradrenergic neurons is inhibited by activation of presynaptic and somatodendritic α_{2A}-adrenoceptors (Starke, 2001). The α_{2A}-adrenoceptor gene (*ADRA2A*) has served as a candidate in ADHD studies also because it is the most prevalent noradrenergic receptor in the prefrontal cortex (Arnsten et al., 1999; Park et al., 2005). Previous investigations have demonstrated that the

C-1291G polymorphism of *ADRA2A* is associated with the severity of ADHD symptoms in clinical samples. Among ADHD patients, subjects with the GG genotype have more often inattentive and combined symptoms (Roman et al., 2003; Schmitz et al., 2006) and G-allele associates with indirect hostility, irritability and verbal aggression in students and with impulsivity in normal adults (Comings et al., 2000). However, so far there is no published evidence of occurring interaction effects of *ADRA2A* genotype and environmental factors on any behavioural variable in humans.

In the present study, significant interaction of family relationships and *ADRA2A* polymorphism on the expression of behavioural outcomes in 15 years old adolescents was found: Boys with the CC genotype and higher score of reported physical and emotional abuse demonstrated significantly more overactive behaviour and concentration difficulties than boys with CC genotype and no maltreatment history, and they also had more inattentive symptoms measured by SNAP-IV (Figure 7). No effect of maltreatment on the behaviour of boys with *ADRA2A* G allele was detected. This result suggests that family relations may act together with genetic factors to develop behavioural problems in adolescence. The regulation of central noradrenergic activity through α_{2A}-adrenoceptors is complex since these receptors serve as somatodendritic autoreceptors, presynaptic auto- and heteroreceptors, and postsynaptic receptors. Noradrenergic activation is limited by α_2-adrenoceptors on the cell bodies and dendrites within locus coeruleus: when the locus coeruleus neurons fire, local release of noradrenaline also occurs, resulting in a decrease of firing of the locus coeruleus neurons. This autoinhibition, mediated by the α_{2A}-adrenoceptor subtype (Callado & Stamford, 1999), can potentially decrease the release of noradrenaline in the projection areas, as prefrontal cortex (Van Gaalen et al., 1997). It is known that α_{2A}-adrenoceptors are also localized both presynaptically on noradrenergic and serotonergic nerve terminals and postsynaptically on the dendritic spines of neurons in prefrontal cortex (Aoki et al., 1998). This multiplicity of functionally important distinct locations serves as a source of non-linear effects if all receptors are affected simultaneously, as by systemic drug treatment or a genetic variant. For example, Arnsten et al. (1999) have described an inverted U shape response to noradrenaline receptor stimulation on cognitive functions. While noradrenergic neurotransmission is crucial for any type of novel information processing, stressful stimuli are known to additionally increase neuronal activity in the locus coeruleus (Abercrombie & Jacobs, 1987) and provide further complexity. Persistent stress reduces the expression of the α_{2A}-adrenoceptor gene transcription in locus coeruleus neurons (Meyer et al., 2000) and leads to an altered balance in noradrenergic neurochemistry. Therefore it has been argued that dysregulation of the locus coeruleus projection activities, brought about by an interplay of genetic and environmental factors, and consequent dysregulation of monoaminergic neurotransmission in general may be responsible for basic impairments in cognitive and emotional processing (Harro & Oreland, 2001). It is possible that stress induced changes in the central

noradrenergic system may have different contribution to cognitive and behavioural changes in individuals with different *ADRA2A* genotype. It could therefore be hypothesised that G allele provides protection for developing hostile behaviour and concentration difficulties in adolescence when maltreatment in the family is present. However, a causal relationship between genetic variants, family relations and behaviour problems cannot be demonstrated by the present study.

Studies on ADHD patients have revealed a possible role of carrying a G allele of the ADRA2A gene. The functional impact of the C-1291G polymorphism of the *ADRA2A* has also been revealed in several physiological studies, some of which suggest that GG homozygotes may further differ from the subjects with the CG genotype regarding some variables. There is evidence that GG homozygotes differ from C allele carriers in measures of carbohydrate metabolism (Rosmond et al., 2002), and children with GG genotype have higher consumption of sweet food (Mäestu et al., 2007). This evidence of physiological significance of the GG genotype gives a reason to believe that it has a different type of impact on behavioural functioning. Furthermore, evidence from our preliminary study indicates that subjects with the GG genotype have significantly slower reaction time in a visual discrimination task (Harro et al., 2007), which implies that this genotype may have a specific impact on the noradrenaline-mediated attentional mechanisms. There is also evidence that the subjects homozygous for the G allele show a tendency to have increased response time variability (Cho et al., 2008). An increased intra-individual variability in response time may be a manifestation of impaired topdown attentional control, which is as underlying cognitive deficits seen in ADHD (Barkley, 1997). As these studies have pointed out the relative importance of GG genotype of C-1291G promoter polymorphism in *ADRA2A* in cognitive processing, physiology and behaviour, we therefore tested it in interaction with family relations on aggression, inattention and hyperactivity, despite of the low number of subjects with this genotype. In girls, but not in boys, the interactions of hostile family environment and *ADRA2A* polymorphism on behaviour were dependent on GG genotype of *ADRA2A* rather than G allele. Girls with GG genotype and no history of maltreatment had significantly more aggressive behaviour and inattention symptoms than physically and emotionally abused girls with the same genotype (Figure 8). We have previously found that *ADRA2A* genotype has an impact on personality traits in adolescents, GG genotype showing higher scores of depressiveness and lower scores of morality and orderliness (Mäestu et al., 2008), but in the present study, maltreated girls with this genotype do not show aggression or signs of inattention even at normal levels. Nevertheless, the small number of participants with the GG genotype in the sample of girls limits any analysis. However, maltreatment in the family had significantly increased aggressiveness and inattention among girls with CC genotype.

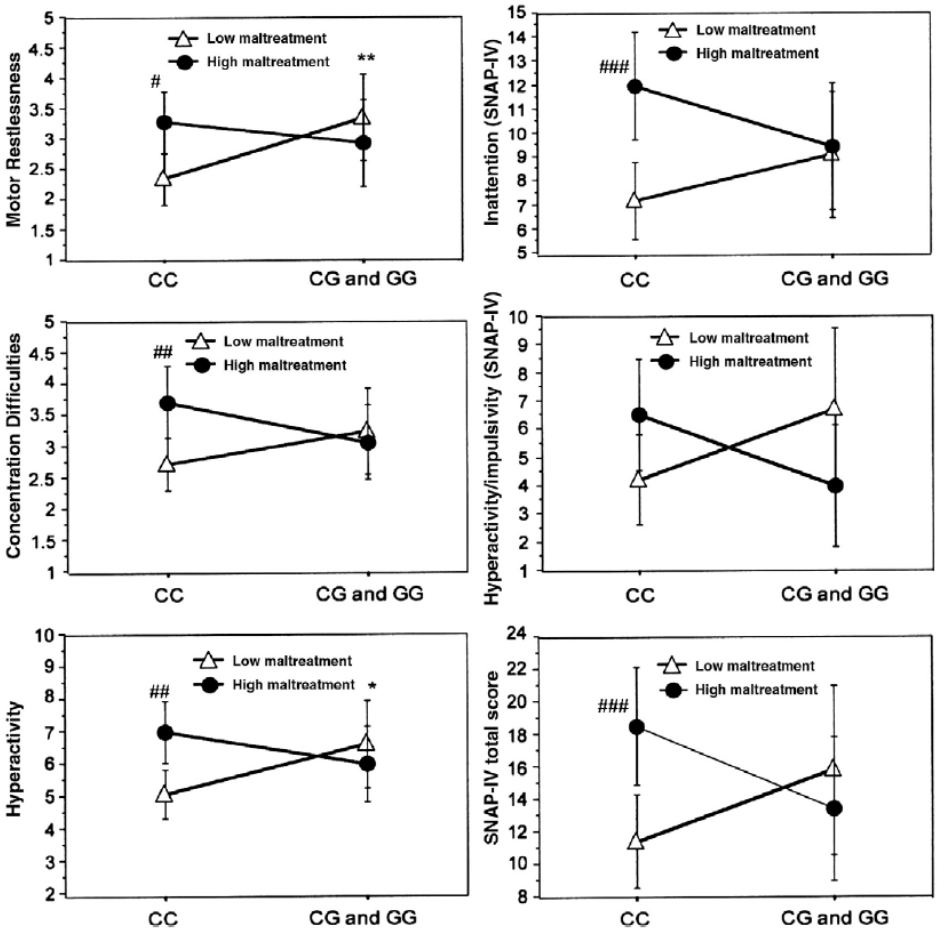

Figure 7. Interaction effects of *ADRA2A* genotype×maltreatment on the scores of Hyperactivity and SNAP-IV subscales in boys. See columns: Hyperactivity refers to the sum of Motor Restlessness and Concentration Difficulties and SNAP-IV total score is the sum of the scores of Inattention and Hyperactivity/Impulsivity. Whiskers indicate 95% confidence intervals. *p<0.05, **p<0.01 G allele vs CC with similar Maltreatment score; #p<0.01, ##p<0.005, ###p<0.001 high vs low maltreatment in CC boys.

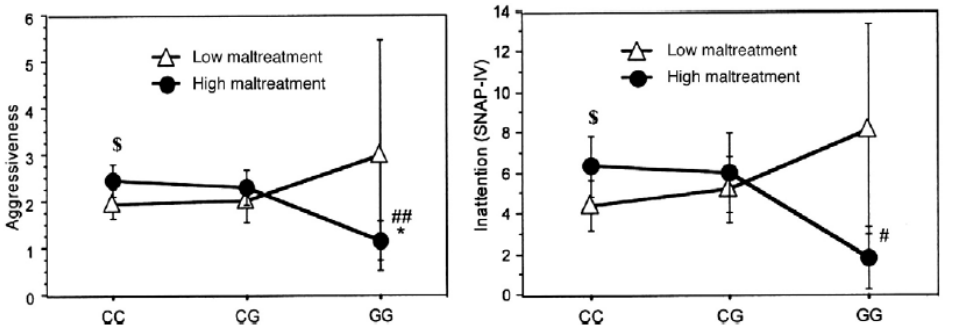

Figure 8. Interaction effects of *ADRA2A* genotype×maltreatment in the family on the scores of Aggressiveness and Inattention in girls. Whiskers indicate 95% confidence intervals. *p<0.05 vs CC with similar Maltreatment score; #p<0.01, ##p<0.005 vs GG+low maltreatment; $p<0.05 vs CC+low maltreatment in the family.

5. CONCLUSIVE REMARKS

Development of the application of molecular genetic strategies to psychiatric genetics started in 1980s and the re-emergence of an interest in gene-environment interplay activated in 1990s (Rutter et al., 2006). However, we are still searching for new genes associated with behavioural phenotypes or psychiatric disorders and are still in our way towards understanding of gene-environment interplay.

In this dissertation we could contribute to this field with new knowledge on gene-environment interplay within a population representative sample adolescents and young adults. Thus, it is possible to generalize our results to healthy people and general population.

5HTTLPR is the most studied genetic variation, as it has significant impact on the structure and function of the brain, with many environment-dependent consequences. We found that adolescents with 5-HTTLPR s-allele are more maladaptively impulsive and less supportive family relations are associated with higher maladaptive impulsivity in s-allele carrying girls. Females with s'-allele are sensitive to issues with important others also after adolescence. The lack of issues with friends and relatives was associated with lower depressiveness in s'-allele young women. Noninterpersonal issues had no impact on their depressiveness asserting the need for more refined and rigorous stress measurement (Monroe & Reid, 2008) that enables to assess interpersonal relations in 5-HTTLPR-behaviour interplay. Thus, family enviroment appears as an important moderator on the effect of 5-HTTLPR on behaviour.

Neuronal nitric oxide synthase is a recently emerged target in studies on impulsivity and related behaviours. In our sample, impulsivity and anxiety related traits were associated with the *NOS1* gene ex1f-VNTR polymorphism. Participants with s-allele had higher neuroticism and s-allele males had higher adaptive impulsivity. Participants with s/s genotype had higher maladaptive impulsivity if they had experienced adversity in the environment. We found also some gender-dependent effects. Males with l/l genotype and females with s-allele presented more anxiety-related traits within more adverse environment. Altogether these findings provide a novel lead to understand the mechanisms that maintain "risk variants" of genes in human population.

The noradrenergic neurotransmission is critically involved in processing novel information from the environment. We discovered that high maltreatment in the family was associated with higher scores in ADHD subscales and low maltreatment was associated with lower scores in ADHD subscales only in adolescents with *ADRA2A* CC genotype.

Thus, good family relations might prevent developing traits associated with psychiatric disorders within adolescents and young adults with malleable genotypes, although single gene x environment effect on behavior is very small at the population level. Therefore, as we can not totally prevent appearing stressful life events in our lives, improving family environment or retaining

good interpersonal relationships might prevent developing maladaptive behavioural traits and help to reveal best traits in subjects with malleable genotype. Therefore, besides gaining more knowledge in association between genes and behaviour, investments should also be made to improve family environment for preventing psychiatric disorders.

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7. REFERENCES

Abercrombie, E.D., Jacobs, B.L. (1987). Single unit response of noradrenergic neurons in the locus coeruleus of freely moving cats: I. Acutely presented stressful and nonstressful stimuli. *Journal of Neuroscience, 7,* 2837–2843.

d'Acremont, M., Linden, M.V.der. (2007). How is impulsivity related to depression in adolescence? Evidence from a French validation of the cognitive emotion regulation questionnaire. *Journal of Adolescence, 30,* 271–282.

af Klinteberg, B. (1988). *Studies on sex-related psychological and biological indicators of psychosocial vulnerability: a developmental perspective.* Department of Psychology, University of Stockholm.

af Klinteberg, B., Oreland, L. (1995). Hyperactive and aggressive behaviors in childhood as related to low platelet monoamine oxidase (MAO) activity at adult age: a longitudinal study of male subjects. *Personality and Individual Differences, 19,* 373–383.

American Psychiatric Association (1994). *Diagnostic and statistical manual of mental disorders.* American Psychiatric Association.

Anchordoquy, H.C., McGeary, C., Liu, L., Krauter, K.S., Smolen, A. (2003). Genotyping of three candidate genes following whole genome preamplification of DNA collected from buccal cells. *Behavior Genetics, 33,* 73–78.

Aoki, C., Venkatesan, C., Go, C.G., Forman, R., Kurose, H. (1998). Cellular and subcellular sites for noradrenergic action in the monkey dorsolateral prefrontal cortex as revealed by the immunocytochemical localization of noradrenergic receptors and axons. *Cerebral Cortex, 8,* 269–277.

Arnsten, A.F. (1999). Development of the cerebral cortex: XIV. Stress impairs prefrontal cortical function. *Journal of the American Academy of Child and Adolescent Psychiatry, 38,* 220–222.

Arnsten, A.F., Li, B.M. (2005). Neurobiology of executive functions: catecholamine influences on prefrontal cortical functions. *Biological Psychiatry, 57,* 1377–1384.

Barkley, RA. (1997). Behavioral inhibition, sustained attention, and executive functions: constructing a unifying theory of ADHD. *Psychological Bulletin, 121,* 65–94.

Bechara, A., Tranel, D., Damasio, H., & Damasio, A.R. (1996). Failure to respond autonomically to anticipated future outcomes following damage to the prefrontal cortex. *Cerebral Cortex, 6,* 215–225.

Belsky, J., Jonassaint, C., Pluess, M., Stanton, M., Brummett, B., Williams, R. (2009). Vulnerability genes or plasticity genes? *Molecular Psychiatry, 14*, 746–754.

Bezdjian, S., Baker, L.A., Tuvblad, C. (2011). Genetic and environmental influences on impulsivity: A meta-analysis of twin, family and adoption studies. *Clinical Psychology Review, 31,* 1209–1223.

Brummett, B.H., Muller, C.L., Collins, A.L., Boyle, S.H., Kuhn, C.M., Siegler, I.C., Williams, R.B., Ashley-Koch, A. (2008). 5-HTTLPR and gender moderate changes in negative affect responses to tryptophan infusion. *Behavioral Genetics, 38,* 476–483.

Callado, L.F., Stamford, J.A. (1999). Alpha2A- but not alpha 2B/C-adrenoceptors modulate noradrenaline release in rat locus coeruleus: voltammetric data. *European Journal Pharmacology, 366,* 35–39.

Canli, T., Congdon, E., Todd Constable, R., Lesch, K.P. (2008). Additive effects of serotonin transporter and tryptophan hydroxylase-2 gene variation on neural correlates of affective processing. *Biological Psychology, 79,* 118–125.

Caspi, A., Moffitt, T.E. (2006). Gene–environment interactions in psychiatry: joining forces with neuroscience. *Nature Reviews Neuroscience, 7,* 583–590.

Caspi, A., Sugden, K., Moffitt, T.E., Taylor, A., Craig, I.W., Harrington, H., McClay, J., Mill, J., Martin, J., Braithwaite, A., Poulton, R. (2003). Influence of life stress on depression: moderation by a polymorphism in the 5-HTT gene. *Science, 301,* 386–389.

Cattell R.B. (1966). The scree test for the number of factors. *Multivariate Behavioral Research, 1,* 245–276.

Cheon, K.A., Cho, D.Y., Koo, M.S., Song, D.H.,Namkoong, K. (2009). Associations between homozygosity of a G allele of the alpha-2a-adrenergic receptor gene andmethylphenidate response in Korean children and adolescents with attention-deficit/hyperactivity disorder. *Biological Psychiatry, 65,* 564–570.

Chioqueta, A.P., Stiles, T.C. (2005). Personality traits and the development of depression, hopelessness, and suicide ideation. *Personality and Individual Differences, 38*, 1283–1291.

Cho, S.C., Kim, J.W., Kim, B.N., Hwang, J.W., Park, M., Kim, S.A., Cho, D.Y., Yoo, H.J., Chung, U.S., Son, J.W., Park, T.W. (2008). Possible association of the alpha-2A-adrenergic receptor gene with response time variability in attention deficit hyperactivity disorder. *American Journal of Medical Genetics Part B:Neuropsychiatric Genetics, 147,* 957–963.

Clarke, H., Flint, J., Attwood, A. S., Munafò, M. R. (2010). Association of the 5-HTTLPR genotype and unipolar depression: A meta-analysis. *Psychological Medicine, 40,* 1767–1778.

Clavarino, A., Hayatbakhsh, M.R., Williams, G.M., Bor, W., O'Callaghan, M., Najman, J.M. (2011). Depression following marital problems: different impacts on mothers and their children? A 21-year prospective study. *Social Psychiatry & Psychiatric Epidemiology, 46,* 833–841.

Comings, D.E., Johnson, J.P., Gonzales, N.S., Huss, M., Saucier, G., McGue, M., MacMurray, J. (2000). Association between the adrenergic alpha 2A receptor gene (ADRA2A) and measures of irritability, hostility, impulsivity and memory in normal subjects. *Psychiatric Genetics, 10,* 39–42.

Corruble, E., Damy, C., Guelfi, J.D. (1999) Impulsivity: a relevant dimension in depression regarding suicide attempts? *Journal of Affective Disorders, 53,* 211–215.

Costa, P.T. Jr, McCrae, R.R. (1989). *The NEO-PI/NEO-FFI manual supplement.* Odessa: Psychological Assessment Resources.

Costa, P.T. Jr., McCrae, R.R. (1992). *Revised NEO personality inventory (NEO-PI-R) and NEO five-factor inventory (NEO-FFI).* Lutz: Psychological Assessment Resources.

Craig, W. (2000). *Childhood social development. The essential readings.* Malden: Blackwell Publishers Ltd.

Crişan, L.G., Pană, S., Vulturar, R., Heilman, R.M., Szekely, R., Drugă, B., Dragoş, N., Miu, A.C. (2009). Genetic contributions of the serotonin transporter to social learning of fear and economic decision making. *Social Cognitive and Affective Neuroscience, 4,* 399–408.

Daruna, J.H., Barnes, P.A. (1993). A neurodevelopmental view on impulsivity. In McCown, W.B., Johnson, J.L., Shure, M.B. (Eds.), *The impulsive client: theory, research and treatment.* Washington, DC: American Psychological Association.

Dickman, S.J. (1990). Functional and dysfunctional impulsivity: personality and cognitive correlates. *Journal of Personality and Social Psychology, 58,* 95–102.

Duncan, L.E., Keller, M.C. (2011). A critical review of the first 10 years of candidate gene-by-environment interaction research in psychiatry. *American Journal of Psychiatry, 168,* 1041–1049.

Ebstein, R.P. (2006). The molecular genetic architecture of human personality: beyond self-report questionnaires. *Molecular Psychiatry, 11,* 427–445.

Eisenberg, N., Chang, L., Ma, Y., Huang, X. (2009). Relations of parenting style to Chinese children's effortful control, ego resilience, and maladjustment. *Development and Psychopathology, 1,* 455–477.

Eley, T.C., Sugden, K., Corsico, A., Gregory, A.M., Sham, P., McGuffin, P., Plomin, R., Craig, I.W. (2004). Gene–environment interaction analysis of serotonin system markers with adolescent depression. *Molecluar Psychiatry, 9,* 908–915.

Eley, T.C., Hudson, J.L., Creswell, C., Tropeano, M., Lester, K.J., Cooper, P., Farmer, A., Lewis, C.M., Lyneham, H.J., Rapee, R.M., Uher, R., Zavos, H.M., Collier, D.A., (2012). Therapygenetics: the 5HTTLPR and response to psychological therapy. *Molecular Psychiatry 17,* 236–237.

El-Sheikh, M., Keiley, M., Erath, S., Dyer, W.J. (2012). Marital conflict and growth in children's internalizing symptoms: The role of autonomic nervous system activity. *Developmental Psychology*. Advance online publication. doi: 10.1037/a0027703

Evenden, J.L. (1999). Varieties of impulsivity. *Psychopharmacology, 146,* 348–361.

Famularo, R., Kinscherff, R., Fenton, T. (1992). Psychiatric diagnoses of maltreated children: preliminary findings. *Journal of the American Academy of Child and Adolescent Psychiatry*, *31,* 863–867.

Faraone, S.V., Perlis, R.H., Doyle, A.E., Smoller, J.W., Goralnick, J.J., Holmgren, M.A., Sklar, P. (2005). Molecular genetics of attention-deficit/hyperactivity disorder. *Biological Psychiatry, 57,* 1313–1323.

Farmer, A., Redman, K., Harris, T., Mahmood, A., Sadler, S., McGuffin, P. (2001). Sensation-seeking, life events and depression. The Cardiff Depression Study. *The British Journal of Psychiatry, 178,* 549–552.

Forssman, L., Eninger, L., Tillman, C.M., Rodriguez, A., Bohlin, G. (2012). Cognitive functioning and family risk factors in relation to symptom behaviors of ADHD and ODD in adolescents. *Journal of Attention Disorders, 16,* 284–294.

Garthwaite, J. (2008). Concepts of neural nitric oxide-mediated transmission. *European Journal of Neuroscience, 27,* 2783–2802.

Geissler, J., Lesch, K.P. (2011). A lifetime of attention-deficit/hyperactivity disorder: diagnostic challenges, treatment and neurobiological mechanisms. *Expert Review of Neurotherapeutics, 11,* 1467–1484.

Gerra, G., Garofano, L., Castaldini, L., Rovetto, F., Zaimovic, A., Moi, G., Bussandri, M., Branchi, B., Brambilla, F., Friso, G., Donnini, C. (2005a). Serotonin transporter promoter polymorphism genotype is associated with temperament, personality traits and illegal drugs use among adolescents. *Journal of Neural Transmission, 112,* 1397–1410.

Gerra, G., Garofano, L., Zaimovic, A., Moi, G., Branchi, B., Bussandri, M., Brambilla, F., Donnini, C. (2005b). Association of the serotonin transporter promoter

polymorphism with smoking behavior among adolescents. *American Journal of Medical Genetics Part B*: *Neuropsychiatric Genetics*, *5,* 73–78.

Gerwitz, J.C., Falls, W.A., Davis, M. (1997). Normal conditioning inhibition and extinction of freezing and fear-potentiated startle following electrolytic lesions of medial prefrontal cortex in rates. *Behavioral Neuroscience, 111,* 712–726.

Goldman, N., Glei, D.A., Lin, Y.H., Weinstein, M. (2010). The serotonin transporter polymorphism (5-HTTLPR): allelic variation and links with depressive symptoms. *Depression & Anxiety, 27,* 260–269.

Grabe, H.J., Lange, M., Wolff, B., Völzke, H., Lucht, M., Freyberger, H.J., John, U., Cascorbi, I. (2005). Mental and physical distress is modulated by a polymorphism in the 5-HT transporter gene interacting with social stressors and chronic disease burden. *Molecular Psychiatry, 10,* 220–224.

Granö, N., Keltikangas-Järvinen, L., Kouvonen, A., Virtanen, M., Elovainio, M., Vahtera, J., Kivimäki, M. (2007). Impulsivity as a predictor of newly diagnosed depression. *Scandinavian Journal of Psychology, 48,* 173–179.

Greenspan, R.J. (1997). A kinder, gentler genetic analysis of behavior: dissection gives way to modulation. *Current Opinion in Neurobiology, 7,* 805–811.

Grijalba, B., Callado, L.F., Meana, J.J., García-Sevilla, J.A., Pazos, A. (1996). Alpha$_2$-adrenoceptor subtypes in the human brain: a pharmacological delineation of [^{3}H]RX-821002 binding to membranes and tissue sections. *European Journal of Pharmacology*, *310,* 83–93.

Grolnick, W. S., Pomerantz, E. M. (2009). Issues and challenges in studying parental control: toward a new conceptualization. *Child Development Perspectives, 3,* 165–170.

Hammen, C., Brennan, P.A., Keenan-Miller, D., Hazel, N.A., Najman, J.M. (2010). Chronic and acute stress, gender, and serotonin transporter gene–environment interactions predicting depression symptoms in youth. *The Journal of Child Psychology and Psychiatry, 51,* 180–187.

Hariri, A.R., Mattay, V.S., Tessitore, A., Kolachana, B., Fera, F., Goldman, D., Egan, M.F., Weinberger, D.R. (2002). Serotonin transporter genetic variation and the response of the human amygdala. *Science, 297,* 400–403.

Harro, M., Eensoo, D., Kiive, E., Merenäkk, L., Alep, J., Oreland, L., Harro, J. (2001). Platelet monoamine oxidase in healthy 9- and 15-years old children: the effect of gender, smoking and puberty. *Progress in Neuro-Psychopharmacology and Biological Psychiatry, 25*, 1497–1511.

Harro, J., Oreland L. (2001). Depression as a spreading adjustment disorder of monoaminergic neurons: a case for primary implication of the locus coeruleus. *Brain Research Reviews, 38,* 79–128.

Harro, J., Paaver, M., Kiive, E., Mäestu, J., Parik, J. (2007). Attention deficit symptoms, visual information processing, and the ADRA2A C-1291C polymorphism in a population derived sample of children and adolescents. *Journal of Neural Transmission, 114,* 85.

Harro, J., Merenäkk, L., Nordquist, N., Konstabel, K., Comasco, E., Oreland, L. (2009). Personality and the serotonin transporter gene: associations in a longitudinal population-based study. *Biological Psychology, 81,* 9–13.

Heils, A., Teufel, A., Petri, S., Stober, G., Riederer, P., Bengel, D., Lesch, K.P. (1996). Allelic variation of human serotonin transporter gene expression. *Journal of Neurochemistry, 66,* 2621–2624.

Herman, A.I., Philbeck, J.W., Vasilopoulos, N.L., Depetrillo, P.B. (2003). Serotonin transporter promoter polymorphism and differences in alcohol consumption behaviour in a college student population. *Alcohol & Alcoholism, 38,* 446–449.

Hettema, J.M., Neale, M.C., Kendler, K.S. (2001). A review and meta-analysis of the genetic epidemiology of anxiety disorders. *American Journal of Psychiatry*, *158,* 1568–1578.

Holmbeck, G.N., Paikoff, R.L., Brooks-Gunn, J. (1995). Parenting Adolescents. Steinberg, L., Silk, J.S. (2002). Parenting adolescents. In M.H. Bornstein (Ed), *Handbook of parenting: Vol.1. children and parenting.* Mahwah: Erlbaum.

Homberg, J.R., Lesch, K.-P. (2011). Looking on the bright side of serotonin transporter gene variation. *Biological Psychiatry, 69,* 513–519.

Hu, X.-Z., Lipsky, R.H., Zhu, G., Akhtar, L.A., Taubman, J., Greenberg, B.D., Xu, K., Arnold, P.D., Richter, M.A., Kennedy, J.L., Murphy, D.L., Goldman, D. (2006). Serotonin transporter promoter gain-of-function genotypes are linked to obsessive-compulsive disorder. *The American Journal of Human Genetics, 78,* 815–826.

Hutchinson, G. T., Patock-Peckham, J. A., Cheong, J., Nagoshi, C. T. (1998). Irrational beliefs and behavioral misregulation in the role of alcohol abuse among college students. *Journal of Rational Emotive and Cognitive Behavior Therapy, 16,* 61–74.

John, O. P., Srivastava, S. (1999). The big five trait taxonomy: History, measurement, and theoretical perspectives. In Pervin, L.A., John, O.P. (Eds.), *Handbook of personality: Theory and research (2nd ed.)*. New York: Guilford.

Johnson, J.G., Cohen, P., Kasen, S., Smailes, E., Brook, J.S. (2001). Association of maladaptive parental behavior with psychiatric disorder among parents and their offspring. *Archives of General Psychiatry, 58,* 453–460.

Karg, K., Burmeister, M., Shedden, K., Sen, S. (2011). The serotonin transporter promoter variant (5-HTTLPR), stress, and depression meta-analysis revisited. Evidence of genetic moderation. *Archives of General Psychiatry, 68,* 444–454.

Karreman, A., de Haas, S., van Tuijl, C., van Aken, M.A., Deković, M. (2010). Relations among temperament, parenting and problem behavior in young children. *Infant Behavior and Development, 33,* 39–49.

Kendler, K.S., Walters, E.E., Neale, M.C., Kessler, R.C., Heath, A.C., Eaves, L.J. (1995). The structure of the genetic and environmental risk factors for six major psychiatric disorders in women. Phobia, generalized anxiety disorder, panic disorder, bulimia, major depression, and alcoholism. *Archives of General Psychiatry, 52,* 374–383.

Kendler, K.S., Karkowski, L.M., Prescott, C.A. (1999). Causal relationship between stressful life events and the onset of a major depression. *American Journal of Psychiatry*, *156*, 837–841.

Kendler, K.S., Thornton, L.M., Prescott, C.A. (2001). Gender differences in the rates of exposure to stressful life events and sensitivity to their depressogenic effects. *The American Journal of Psychiatry, 158,* 587–593.

Kendler, K.S., Greenspan, R.J. (2006). The nature of genetic influences on behavior: lessons from "simpler" organisms. *The American Journal of Psychiatry, 163,* 1683–1694.

Kessler, R.C., McLeod, J.D. (1984). Sex differences in vulnerability to undesirable life events. *American Sociological Review, 49,* 620–631.

Kessler, R.C. (1997). The effects of stressful life events on depression. *Annual Review of Psychology, 48,* 191–214.

Khaleque, A., Rohner, R.P. (2002). Perceived parental acceptance-rejection and psychological adjustment: A meta-analysis of cross-cultural and intracultural studies. *Journal of Marriage and Family, 64,* 54–64.

Kiive, E. Harro, J. (2012). The effect of serotonin transporter gene promoter polymorphism on adolescent and adult ADHD symptoms and educational attainment: A longitudinal study. *European Psychiatry,* in press.

Kim Park, I.J., Garber, J., Ciesla, J.A., Ellis, B.J. (2008). Convergence among multiple methods of measuring positivity and negativity in the family environment: relation to depression in mothers and their children. *Journal of Family Psychology, 22,* 123–134.

Kim, Y.-K. (2009). *Handbook of behavior genetics.* Athens, GA: Springer.

Kim, S., Lee, D. (2011). Prefrontal cortex and impulsive decision making. *Biological Psychiatry, 69,* 1140–1146.

Kinnally, E.L., Huang, Y.Y., Haverly, R., Burke, A.K. Brent, D.A., Oquendo, M.A., Galfalvy, H., Mann, J.J. (2009). Parental care moderates the influence of MAOA-uVNTR genotype and childhood stressors on trait impulsivity and aggression in adult women. *Psychiatric Genetics, 19,* 126–133.

Kiss, J.P., Vizi, E.S. (2001). Nitric oxide: a novel link between synaptic and non-synaptic transmission. *Trends in Neurosciences, 24,* 211–215.

Kling, K.C., Ryff, C.D., Love, G., Essex, M. (2003). Exploring the influence of personality on depressive symptoms and self-esteem across a significant life transition. *Journal of Personality and Social Psychology, 85,* 922–932.

Konstabel, K., Lönnqvist, J.-L., Walkowitz, G., Konstabel, K., Verkasalo, M. (2012). The "Short Five" (S5): measuring personality traits using comprehensive single items. *European Journal of Personality, 26,* 13–29.

Kriegebaum, C., Gutknecht, L., Schmitt, A., Lesch, K.P., Reif, A. (2010). Serotonin now: Part 2. Behavioral genetics and psychopathology. *Fortschritte der Neurologie-Psychiatrie, 78,* 332–342.

Lafontan, M., Berlan, M. (1993). Fat cell adrenergic receptors and the control of white and brown fat cell function. *The Journal of Lipid Research, 34,* 1057–1092.

Lage, G.M., Malloy-Diniz, L.F., Matos, L.O., Bastos, M.A., Abrantes, S.S., Corrêa, H. (2011). Impulsivity and the 5-HTTLPR polymorphism in a non-clinical sample. *PLoS One, 6,* e16927.

Lario, S., Calls, J., Cases, A., Oriola, J., Torras, A., Rivera, F. (1997). MspI identifies a biallelic polymorphism in the promoter region of the 2A-adrenergic receptors. *Clinical Genetics, 51,* 129–130.

Leadbeater, B.J., Kuperminc, G.P., Blatt, S.J., Hertzog, C. (1999). A multivariate model of gender differences in adolescents' internalizing and externalizing problems. *Developmental Psychology, 35,* 1268–1282.

Lengua, L.J., Wolchik, S.A., Sandler, I.N., West, S.G. (2010). The additive and interactive effects of parenting and temperament in predicting adjustment problems of children of divorce. *Journal of Clinical Child Psychology, 29,* 232–244.

Lenroot, R.K., Giedd, J.N. (2011). Annual Research Review: Developmental considerations of gene by environment interactions. *Journal of Child Psychology and Psychiatry. Special Issue: Annual Research Review issue, 52,* 429–441.

Lesch, K.P., Wolozin, B.L., Estler, H.C., Murphy, D.L., Riederer, P. (1993). Isolation of a cDNA encoding the human brain serotonin transporter. *Journal of Neural Transmission, 91,* 67–72.

Lesch, K.P., Bengel, D., Heils, A., Sabol, S.Z., Greenberg, B.D., Petri, S., Benjamin, J., Muller, C.R., Hamer, D.H., Murphy, D.L. (1996). Association of anxiety-related traits with a polymorphism in the serotonin transporter gene regulatory region. *Science, 274,* 1527–1531.

Lesch, K.P., Merschdorf, U. (2000). Impulsivity, aggression, and serotonin: a molecular psychobiological perspective. *Behavioral Sciences & the Law*, *18,* 581–604.

Lesch, K.P. (2004). Gene-environment interaction and the genetics of depression. *Journal of Psychiatry and Neuroscience*, *29,* 174–184.

Lesch, K.P., Gutknecht, L. (2005). Pharmacogenetics of the serotonin transporter. *Progress in Neuro-Psychopharmacology and Biological Psychiatry, 29,* 1062–1073.

Lesch, K.-P. (2007). Linking emotion to the social brain. The role of the serotonin transporter in human social behaviour. *EMBO reports, 8,* S24–S29.

Li, D., He, L. (2007). Meta-analysis supports association between serotonin transporter (5-HTT) and suicidal behavior. *Molecular Psychiatry, 12,* 47–54.

López-León, S., Janssens, A.C., Gonzáles-Zuloeta Ladd, A.M., Claes, S.J., Oostra, B.A., van Duijn, C.M. (2008). Meta-analyses of genetic studies on major depression disorder. *Molecular Psychiatry, 13,* 772–785.

Mäestu, J., Villa, I., Parik, J., Paaver, P., Merenäkk, L., Eensoo, D, Harro, M., Harro, J. (2007). Human adrenergic alpha2A receptor C-1291G polymorphism leads to higher consumption of sweet food products. *Molecular Psychiatry, 12,* 520–521.

Mäestu, J., Allik, J., Merenäkk, L., Eensoo, D., Parik, J., Veidebaum, T., Harro, J. (2008). Associations between an alpha 2a adrenergic receptor gene polymorphism and adolescent personality. *American Journal of Medical Genetics Part B*: *Neuro-psychiatric Genetics, 147,* 418–423.

Magnusson, D., Duner, A., Zetterblom, G. (1975). *Adjustment: a longitudinal study*. Stockholm: Almquist & Wiksell.

McDermott, Jr,J., Robillard, A.B., Char, W.F., Hsu, J., Tzeng, W., Ashton, G.C. (1983). Reexamining the concept of adolescence: differences between adolescent boys and girls in the context of their families. *American Journal of Psychiatry, 14,* 1318–1322.

Merenäkk, L., Mäestu, J., Nordquist, N., Parik, J., Oreland, L., Loit, H.M., Harro, J. (2011). Effects of the serotonin transporter (5-HTTLPR) and α2A-adrenoceptor (C-1291G) genotypes on substance use in children and adolescents: a longitudinal study. *Psychopharmacology, 215,* 13–22.

Meyer, J.S., Quenzer, L.F. (2005). *Psychopharmacology: drugs, the brain, and behavior*. Sunderland: Sinauer Associates.

Meyer, H., Palchaudhuri, M., Scheinin, M., Flügge, G. (2000). Regulation of alpha(2A)-adrenoceptor expression by chronic stress in neurons of the brain stem. *Brain Research, 880,* 147–158.

Minelli, A., Bonvicini, C., Scassellati, C., Sartori, R., Gennarelli, M. (2011). The influence of psychiatric screening in healthy populations selection: a new study and meta-analysis of functional 5-HTTLPR and rs25531 polymorphisms and anxiety-related personality traits. *BMC Psychiatry, 11,* 50.

Moeller, F.G., Barratt, E.S., Dougherty, D.M., Schmitz, J.M., Swann, A.C. (2001). Psychiatric aspects of impulsivity. *The American Journal of Psychiatry, 158,* 1783–1793.

Monroe, S.M., Reid, M.W. (2008). Gene-environment interactions in depression research: genetic polymorphisms and life-stress polyprocedures. *Psychological Science, 19,* 947–956.

Montgomery, S.A., Åsberg, M. (1979). A new depression scale designed to be sensitive to change. *The British Journal of Psychiatry, 134*, 382–389.

Morgan, M.A., Romanski, L.M., LeDoux, J.E. (1993). Extinction of emotional learning: Contribution of medial prefrontal cortex. *Neuroscience Letters, 163,* 109–113.

Morgan, K., Norris, G. (2010). An exploration into the relevance of Dickman's functional and dysfunctional impulsivity dichotomy for understanding ADHD-type behaviors. *Individual Differences Research, 8,* 34–44.

Mõttus, R., Pullmann, H., Allik, J. (2006). Towards more readable Big Five personality inventories. *European Journal of Psychological Assessment, 22*, 149–157.

Mulder, M.J., Bos, D., Weusten, J.M., van Belle, J., van Dijk, S.C., Simen, P., van Engeland, H., Durston, S. (2010). Basic impairments in regulating the speed-accuracy tradeoff predict symptoms of attention-deficit/hyperactivity disorder. *Biological Psychiatry, 15,* 1114–1119.

Nelson C.A. (2006). Neurobehavioral development in the context of biocultural co-constructivism. In Baltes P.B., Reuter-Lorenz P.A., Rösler F. (Eds.), *Lifespan development and the brain: the perspective of biocultural co-constructivism.* New York: Cambridge University Press.

Neumann, A., Barker, E.D., Koot, H.M., Maughan, B. (2010). The role of contextual risk, impulsivity, and parental knowledge in the development of adolescent antisocial behavior. *Journal of Abnormal Psychology, 119,* 534–545.

Neumeister, A., Konstantinidis, A., Stastny, J., Schwarz, M.J., Vitouch, O., Willeit, M., Praschak-Rieder, N., Zach, J., de Zwaan, M., Bondy, B., Ackenheil, M., Kasper, S. (2002). Association between serotonin transporter gene promoter polymorphism (5HTTLPR) and behavioral responses to tryptophan depletion in healthy women with and without family history of depression. *Archives of General Psychiatry, 59,* 613–620.

Olson, S.L., Bates, J.E., Bayles, K. (1990). Early antecedents of childhood impulsivity: the role of parent-child interaction, cognitive competence, and temperament. *Journal of Abnormal Child Psychology, 18,* 317–334.

Olson, S.L., Bates, J.E., Sandy, J.M., Schilling, E.M. (2002). Early developmental precursors of impulsive and inattentive behavior: from infancy to middle childhood. *Journal of Child Psychology and Psychiatry, 43,* 435–447.

Ouyang, L., Fang, X., Mercy, J., Perou, R., Grosse, S.D. (2008). Attention deficit/ hyperactivity disorder symptoms and child maltreatment: a population-based study. *The Journal of Pediatrics, 153,* 851–856.

Paaver, M., Nordquist, N., Parik, J., Harro, M., Oreland, L., Harro, J. (2007). Platelet MAO activity and the 5-HTT gene promoter polymorphism are associated with impulsivity and cognitive style in visual information processing. *Psychopharmacology, 194,* 545–554.

Park, L., Nigg, J., Waldman, I.D., Nummy, K.A., Huang-Pollock, C., Rappley, M., Friderici, K.H. (2005). Association and linkage of α-2A adrenergic receptor gene polymorphisms with childhood ADHD. *Molecular Psychiatry, 10,* 572–580.

Patton, J. H., Stanford, M. S., Barratt, E. S. (1995). Factor structure of the Barratt Impulsiveness Scale. *Journal of Clinical Psychology*, *51,* 768–774.

Perugi, G., Del Carlo, A., Benvenuti, M., Fornaro, M., Toni, C., Akiskal, K., Dell'Osso, L., Akiskal, H. (2011). Impulsivity in anxiety disorder patients: is it related to comorbid cyclothymia? *Journal of Affective Disorders, 133,* 600–606.

Peterson, J.L., Zill, N. (1986). Marital disruption, parent-child relationships, and behavior problems in children. *Journal of Marriage and Family, 48,* 295–307.

Polanczyk, G., Zeni, C., Genro, J.P., Guimarães, A.P., Roman, T., Hutz, M.H., Rohde, L.A. (2007). Association of the adrenergic alpha 2A receptor genewithmethylphenidate improvement of inattentive symptoms in children and adolescents with attention-deficit/hyperactivity disorder. *Archives of General Psychiatry, 64,* 218–224.

Pulver, A., Allik, J., Pulkkinen, L., Hämäläinen, M. (1995). A big five personality inventory in two non-indo-european languages. *European Journal of Personality, 9,* 109–124.

Reif, A., Herterich, S., Strobel, A., Ehlis, A.-C., Saur, D., Jacob, C.P., Wienker, T., Töpner, T., Fritzen, S., Walter, U., Schmitt, A., Fallgatter, A.J., Lesch, K.-P. (2006). A neuronal nitric oxide synthase (NOS-I) haplotype associated with schizophrenia modifies prefrontal cortex function. *Molecular Psychiatry, 11*, 286–300.

Reif, A., Jacob, C.P., Rujescu, D., Herterich, S., Lang, S., Gutknech, L., Baehne, C.G., Strobel, A., Freitag, C.M., Giegling, I., Romanos, M., Hartmann, A., Rösler, M., Renner, T.J., Fallgatter, A.J., Retz, W., Ehlis, A.-C., Lesch, K.-P. (2009). Influence of functional variant of neuronal nitric oxide synthase on impulsive behaviors in humans. *Archives of General Psychiatry, 66*, 41–50.

Repetti, R.L., Taylor, S.E., Seeman, T.E. (2002). Risky families: family social environments and the mental and physical health of offspring. *Psychological Bulletin, 128,* 330–366.

Rettew, D.C., Vink, J.M., Willemsen, G., Doyle, A., Hudziak, J.J., Boomsma, D.I. (2006). The genetic architecture of neuroticism in 3301 Dutch adolescent twins as a function of age and sex: a study from the Dutch twin register. *Twin Research and Human Genetics*, *9,* 24–29.

Rice, F. (2009). The genetics of depression in childhood and adolescence. *Current Psychiatry Reports, 11,* 167–173.

Rife, T., Rasoul, B., Pullen, N., Mitchell, D., Grathwol, K., Kurth, J. (2009). The effect of a promoter polymorphism on the transcription of nitric oxide synthase 1 and its relevance to Parkinson's disease. *Journal of Neuroscience Research, 87*, 2319–2325.

Risch, N., Herrell, R., Lehner, T., Liang, K.Y., Eaves, L., Hoh, J., Griem, A., Kovacs, M., Ott, J., Merikangas, K.R. (2009). Interaction between the serotonin transporter gene (5-HTTLPR), stressful life events, and risk of depression: a meta-analysis. *JAMA: The Journal Of The American Medical Association, 301,* 2462–2471.

Roche, K.M., Ahmed, S., Blum, R.W. (2008). Enduring consequences of parenting for risk behaviors from adolescence into early adulthood. *Social Science & Medicine, 66,* 2023–2034.

Rohner, R.P., Khaleque, A. (2005). Parental acceptance–rejection/control questionnaire (PARQ/Control): test manual. In Rohner, R.P., Khaleque, A. (Eds.), *Handbook for the study of parental acceptance and rejection.* Storrs: Rohner Research Publications.

Roman, T., Schmitz, M., Polanczyk, G.V., Eizirik, M., Rohde, L.A., Hutz, M.H. (2003). Is the alpha-2A adrenergic receptor gene (ADRA2A) associated with attention-deficit/hyperactivity disorder? *American Journal of Medical Genetics Part B: Neuropsychiatric Genetics, 120,* 116–120.

Rosmond, R., Bouchard, C., Björntorp, P. (2002). A C-1291G polymorphism in the alpha2A adrenergic receptor gene (ADRA2A) promoter is associated with cortisol escape from dexamethasone and elevated glucose levels. *Journal of Internal Medicine, 251,* 252–257.

Rutter, M., Moffitt, T.E., Caspi, A. (2006). Gene–environment interplay and psychopathology: multiple varieties but real effects. *Journal of Child Psychology and Psychiatry, 47,* 226–261.

Scheibner, J., Trendelenburg, A., Hein, L., Starke, K. (2001). Alpha(2)-adrenoceptors modulating neuronal serotonin release: a study in alpha(2)-adrenoceptor subtype-deficient mice. *British Journal of Pharmacology, 132,* 925–933.

Scheier, M.F., Carver, C.S., Bridges, M.W. (1994). Distinguishing optimism from neuroticism (and trait anxiety, self-mastery, and self-esteem): a reevaluation of the Life Orientation Test. *Journal of Personality and Social Psychology, 67,* 1063–1078.

Schmitz, M., Denardin, D., Silva, E.L., Pianca, T., Roman, T., Hutz, M.H., Faraone, S.V., Rohde, L.A. (2006). Association between alpha-2a-adrenergic receptor gene and ADHD inattentive type. *Biological Psychiatry, 60,* 1028–1033.

Schürks, M., Rist, P.M., Kurth, T. (2010). 5-HTTLPR polymorphism in the serotonin transporter gene and migraine: a systematic review and meta-analysis. *Cephalalgia, 30,* 1296–1305.

Sen, S., Burmeister, M., Ghosh, D. (2004). Meta-analysis of the association between a serotonin transporter promoter polymorphism (5-HTTLPR) and anxiety-related personality traits. *American Journal Of Medical Genetics. Part B, Neuropsychiatric Genetics: The Official Publication Of The International Society Of Psychiatric Genetics, 127B,* 85–89.

Sheeber, L., Hops, H., Alpert, A., Davis, B., Andrews, J. (1997). Family support and conflict: Prospective relations to adolescent depression. *Journal of Abnormal Child Psychology, 25,* 333–344.

Sheese, B.E., Voelker, P.M., Rothbart, M.K., Posner, M.I. (2007). Parenting quality interacts with genetic variation in dopamine receptor D4 to influence temperament in early childhood. *Developmental Psychopathology, 19,* 1039–1046.

Sheline, Y.I., Barch, D.M., Donnelly, J.M., Ollinger, J.M., Snyder, A.Z., Mintun, M.A. (2001). Increased amygdala response to masked emotional faces in depressed subjects resolves with antidepressant treatment: an fMRI study. *Biological Psychiatry, 50,* 651–658.

Shih, J.H., Eberhart, N.K., Hammen, C.L., Brennan, P.A. (2006). Differential exposure and reactivity to interpersonal stress predict sex differences in adolescent depression. *Journal of Clinical Child & Adolescent Psychology, 35,* 103–115.

Shorter, E. (1997). *A history of psychiatry: from the era of the asylum to the age of prozac.* New York: John Wiley & Sons, Inc.

Siegle, G.J., Thompson, W., Carter, C.S., Steinhauer, S.R., Thase, M.E. (2007). Increased amygdala and decreased dorsolateral prefrontal BOLD responses in unipolar depression: related and independent features. *Biological Psychiatry, 61,* 198–209.

da Silva, T.L., Pianca, T.G., Roman, T., Hutz, M.H., Faraone, S.V., Schmitz, M., Rohde, L.A. (2008). Adrenergic α2A receptor gene and response to methylphenidate in attention-deficit/hyperactivity disorder – predominantly inattentive type. *Journal of Neural Transmission, 115,* 341–345.

Sjöberg, R.L., Nilsson, K.W., Nordquist, N., Öhrvik, J., Leppert, J., Lindström, L., Oreland, L. (2006). Development of depression: sex and the interaction between environment and a promoter polymorphism of the serotonin transporter gene. *The International Journal of Neuropsychopharmacology, 9,* 1–7.

Skinner, E., Johnson, S., Snyder, T. (2005). Six dimensions of parenting: a motivational model. *Parenting: Science and Practice, 5,* 175–235.

Sonuga-Barke, E.J.S., Lasky-Su, J., Neale, B.M., Oades, R., Chen, W., Franke, B., Buitelaar, J., Banaschewski, T., Ebstein, R., Gill, M., Anney, R., Miranda, A., Mulas, F., Roeyers, H., Rothenberger, A., Sergeant, J., Steinhausen, H.C., Thompson, M., Asherson, P., Faraone, S.V. (2008). Does parental expressed emotion-moderate genetic effects in ADHD? An exploration using a genome wide association scan. *American Journal of Medical Genetics Part B: Neuropsychiatric Genetics*, *147,* 1359–1368.

Spielberger, C.D. (1966). *Anxiety and behavior.* New York: Academic Press.

Spielberger, C.D. (1983). *Manual for the State-Trait Anxiety Inventory (STAI)*. Palo Alto: Consulting Psychologists Press.

Starke, K. (2001). Presynaptic autoreceptors in the third decade: focus on alpha2-adrenoceptors. *Journal of Neurochemistry, 78,* 685–693.

Steinberg, L., Silk, J.S. (2002). Parenting adolescents. In M.H. Bornstein (Ed.), *Handbook of parenting: Vol.1. children and parenting (2nd ed.).* Mahwah: Erlbaum.

Straus, M.A., Mouradian, V.E. (1998). Impulsive corporal punishment by mothers and antisocial behavior and impulsiveness of children. *Behavioral Sciences and the Law, 16,* 353–374.

Surtees, P.G., Wainwright, N.W., Willis-Owen, S.A., Luben, R., Day, N.E., Flint, J. (2006). Social adversity, the serotonin transporter (5-HTTLPR) polymorphism and major depressive disorder. *Biological Psychiatry, 59,* 224–229.

Suslow, T., Konrad, C., Kugel, H., Rumstadt, D., Zwitserlood, P., Schöning, S., Ohrmann, P., Bauer, J., Pyka, M., Kersting, A., Arolt, V., Heindel, W., Dannlowski, U. (2010). Automatic mood-congruent amygdala responses to masked facial expressions in major depression. *Biological Psychiatry, 67,* 155–160.

Swanson, J.M., Kraemer, H.C., Hinshaw, S.P., Arnold, L.E., Conners, C.K., Abikoff, H.B. (2001). Clinical relevance of the primary findings of the MTA: success rates based on severity of ADHD and ODD symptoms at the end of treatment. *Journal of the American Academy of Child and Adolescent Psychiatry, 40,* 168–179.

Zemore, R., Rinholm, J. (1989). Vulnerability to depression as a function of parental rejection and control. *Canadian Journal of Behavioural Science/Revue canadienne des sciences du comportement, 21,* 364–376.

Zhang, J., Huang, X.Y., Ye, M.L., Luo, C.X., Wu, H.Y., Hu, Y., Zhou, Q.G., Wu, D.L., Zhu, L.J., Zhu, D.Y. (2010). Neuronal nitric oxide synthase alteration accounts for the role of 5-HT1A receptor in modulating anxiety-related behaviors. *Journal of Neuroscience 30*, 2433–2441.

Thapar, A., McGuffin, P. (1997). Anxiety and depressive symptoms in childhood – a genetic study of comorbidity. *The Journal of Child Psychology and Psychiatry, 38,* 651–656.

Tomson, K., Merenäkk, L., Loit, H.-M., Mäestu, J., Harro, J. (2011). The relationship between serotonin transporter gene promoter polymorphism and serum lipid levels at young age in a longitudinal population-representative study. *Progress in Neuro-Psychopharmacology and Biological Psychiatry, 35,* 1857–1862.

Trainor, B.C., Workman, J.L., Jessen, R., Nelson, R.J. (2007). Impaired nitric oxide synthase signaling dissociates social investigation and aggression. *Behavioral Neuroscience, 121,* 362–369.

Tulviste, T. (2012). The relationship among perceived parental acceptance, fathers' involvement in adolescents' life, and the psychological adjustment, depression, and

alcohol use of estonian adolescents. In Ripoll-Núñez, K.J., Comunian, A.L., Brown, C.M. (Eds.), *Expanding horizons: Current research on interpersonal acceptance.* Boca Raton: BrownWalker Press

Tulviste, T., Rohner, R.P. (2010). Relationships between perceived teachers' and parental behavior and adolescent outcomes in Estonia. *Cross-Cultural Research, 44,* 222–238.

Ueno, S. (2003). Genetic polymorphisms of serotonin and dopamine transporters in mental disorders. *Journal of Medical Investigation, 50,* 25–31.

Uher, R., McGuffin, P. (2008). The moderation by the serotonin transporter gene of environmental adversity in the aetiology of mental illness: review and methodological analysis. *Molecular Psychiatry, 13,* 131–146.

Uher, R., McGuffin, P. (2010). The moderation by the serotonin transporter gene of environmental adversity in the etiology of depression: 2009 update. *Molecular Psychiatry, 15,* 18–22.

Van Gaalen, M., Kawahara, H., Kawahara, Y., Westerink, B.H. (1997). The locus coeruleus noradrenergic system in the rat brain studied by dual probe microanalysis. *Brain Research, 763,* 56–62.

Wakeno, M., Kato, M., Okugawa, G., Fukuda, T., Hosoi, Y., Takekita, Y., Yamashita, M., Nonen, S., Azuma, J., Kinoshita, T. (2008). The alpha 2A-adrenergic receptor gene polymorphism modifies antidepressant responses to milnacipran. *Journal of Clinical Psychopharmacology, 28,* 518–524.

Wang, B., Wang, Y., Zhou, R., Li, J., Qian, Q., Yang, L., Guan, L., Faraone, S.V. (2006). Possible association of the alpha-2A adrenergic receptor gene (ADRA2A) with symptoms of attention-deficit/ hyperactivity disorder. *American Journal of Medical Genetics Part B*: *Neuropsychiatric Genetics*, *141,* 130–134.

Wittchen, H.U., Jacobi, F., Rehm, J., Gustavsson, A., Svensson, M., Jönsson, B., Olesen, J., Allgulander, C., Alonso, J., Faravelli, C., Fratiglioni, L., Jennum, P., Lieb, R., Maercker, A., van Os, J., Preisig, M., Salvador-Carulla, L., Simon, R., Steinhausen, H.C. (2011). The size and burden of mental disorders and other disorders of the brain in Europe 2010. *European Neuropsychopharmacology, 21,* 655–679.

Wray, N.R., James, M.R., Gordon, S.D., Dumenil, T., Ryan, L., Coventry, W.L., Statham, D.J., Pergadia, M.L., Madden, P.A., Heath, A.C., Montgomery, G.W., Martin, N.G. (2009). Accurate, large-scale genotyping of 5HTTLPR and flanking single nucleotide polymorphisms in an association study of depression, anxiety, and personality measures. *Biological Psychiatry, 66,* 468–476.

Xu, C., Schachar, R., Tannock, R., Roberts, W., Malone, M., Kennedy, J.L., Barr, C.L. (2001). Linkage study of the alpha2A adrenergic receptor in attention-deficit hyperactivity disorder families. *American Journal of Medical Genetics, 105,* 159–162.

8. SUMMARY IN ESTONIAN

Inimestevaheliste suhete mõju käitumisele sõltuvalt geneetilistest eripäradest

Tänapäeval ollakse üldiselt üksmeelselt seisukohal, et käitumisjoonte kujunemist mõjutavad nii geenid kui keskkond. Siiski on meie teadmised sellest, millised geenid milliste käitumisjoontega seonduvad ning kuidas keskkond neid seoseid mõjutab, veel üsna puudulikud. Oma väitekirjas kajastatud uuringutega püüangi lisada killukese uut informatsiooni pidevalt täienevasse ja uuenevasse käitumisgeneetika valdkonda.

Väitekirjas kajastatud uuringud on läbi viidud Tartu linna ja maakonna noorukite ja noorte täiskasvanute esinduslikul valimil. Uurisin kolme geeni mõju käitumisele ning kas keskkonnategurina peresuhted geeni ja käitumise vahelist seost mõjutavad. Üks seni enimuuritud geenivariant on serotoniini transporteri promooteri piirkonna polümorfism (5-HTTLPR), mille mõju impulsiivsusele sõltuvalt keskkonnast pole esinduslikul valimil siiski veel uuritud. Leidsin, et selle geeni s-alleeliga noorte pidurdamatuse skoorid olid suuremad l/l genotüübiga noorte skooridest. Ilmnes ka geeni ja käitumise vahelise seose sõltuvus keskkonnateguritest. Nimelt s-alleeliga neiud, keda nende perekond vähem toetas, olid oma hinnangu kohaselt suurema mitteadaptiivse impulsiivsusega ehk mõtlematu ja pidurdamatu käitumisega **(I uurimus)**. Ka varases täiskasvanueas avaldasid suhted lähedaste inimestega s'-alleeliga noortele naisterahvastele rohkem mõju. Kui probleemid s'-alleeliga noorte naiste läbisaamist oma lähedastega ei varjutanud, kui nad polnud viimase aasta jooksul pidanud üle elama oma lähedaste kaotust või kokku puutunud lähedaste tõsiste terviseprobleemidega, oli nende depressiivsuse skoor võrreldes teiste uuritud naistega tunduvalt madalam. Probleemide puudumine valdkondades, mis suhteid otseselt ei hõlmanud – näiteks töökoha kaotus, rahalised probleemid, õnnetustesse sattumine – s'-alleeliga naiste depressiivsuse skoore ei vähendanud. Mehed olid stressirikkale keskkonnale tundlikud siis kui neil oli l'/l' genotüüp ning meeste depressiivsust vähendas või suurendas igat tüüpi probleemiderohke keskkonna puudumine või olemasolu **(II uurimus)**. Seega ilmnes, et geeni, keskkonna ja käitumise omavaheliste seost uurimisel on oluline silmas pidada, milliseid keskkonnategureid käsitletakse.

Teise geenivariandina on impulsiivsuse uurimisel hiljuti oluliseks osutunud lämmastikoksiidi süntaasi ex1f-VNTR polümorfism. Leidsime, et selle polümorfismi s-alleeli kandjate neurootilisus oli kõrgem. Kui s-alleeli kandjaks olid mehed, olid ka nende ekstravertsuse **(IV uurimus)** ja adaptiivse impulsiivsuse skoorid kõrgemad, s.t nad olid elamustejanulisemad ja kiirema otsustusstiiliga. Kui u 18-aasta vanuste uuritavate peresuhted olid halvad, siis s/s genotüübiga noorte mitteadaptiivse impulsiivsuse skoorid olid kõrgemad kui teistel uuritavatel **(III uurimus)**. Ebasoodne keskkond suurendas ka s-alleeliga neidude ja l/l genotüübiga noormeeste ärevusega seotud käitumisjooni **(IV uurimus)**.

Selline tulemus meeste puhul seletab ära, miks ebasoodsate käitumisviisidega seotud geenivariandid populatsioonis siiski edasi püsivad: nimelt leidsime, et s/s genotüübiga nooremehed tegutsevad ebasoodsa keskkonna puhul tagajärgedele mõtlemata ja pidurdamatult, mistõttu nad võivad kergesti probleemidesse sattuda. Samas kui neid ümbritsev keskkond on toetav, näiteks toetavate ja soojade peresuhete näol, on s/s genotüübiga noormehed kõige ekstravertsemad, kõige kiirema otsustusstiili ja suurema elamustejanuga, mis võib tihtipeale paremat toimetulekut soosida.

Viimaseks leidsime, et ka kolmanda uuritud geenivariandi ja impulsiivsusega seotud käitumisjoonte vahelist seost mõjutavad peresuhted. Ilmnes, et peres esineva vägivalla ja alavääristamise korral oli ADRA2A geeni CC genotüübiga noortel rohkem aktiivsus- ja tähelepanuhäire sümptomeid, vägivalla- ja alavääristamisevabade peresuhete puhul oli sama genotüübiga noortel aktiivsus- ja tähelepanuhäire sümptomeid märgatavalt vähem. Geen G-alleeli kandjaid halvad peresuhted ei mõjutanud **(V uurimus)**.

Seega, heade peresuhete olemasolul võivad riskigenotüübiga noorte ebasoodsad käitumisjooned esile mitte tõusta, mis näitab peresuhete olulisust ka geeni-käitumise interaktsiooni puhul.

9. PUBLICATIONS

CURRICULUM VITAE

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2004–2006	Master's studies, Department of Public Health, University of Tartu
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Professional employment:

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2009–2011	research fellow, Department of Psychology, University of Tartu
2006–2008	extraordinary research fellow, Department of Psychology, University of Tartu
2005	laboratory assistant, Department of Psychology, University of Tartu
2004–2006	school psychologist, Viluste Basic School
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2001–2004	assistant in different scientific projects for University of Tartu

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Teadustegevus:
Peamised uurimisvaldkonnad: impulsiivsus, depressiivsus, peresuhted, geenid

Kuulumine erialastesse organisatsioonidesse:
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