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KELLI LEHTO

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Department of Psychology, University of Tartu, Estonia

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CONTENTS

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This dissertation is based on the following original publications, further referred to by respective Roman numerals:

I. **Hiio, K**., Merenäkk, L., Nordquist, N., Parik, J., Oreland, L., Veidebaum, T., Harro, J. (2011). Effects of serotonin transporter promoter and BDNF Val66Met genotype on personality traits in a population representative sample of adolescents. *Psychiatric Genetics* 21(5), 261–264.

II. **Lehto, K**., Akkermann, K., Parik, J., Veidebaum, T., Harro, J. (2013). Effect of COMT Val158Met polymorphism on personality traits and educational attainment in a longitudinal population representative study. *European Psychiatry* 28(8), 492–498.

III. **Lehto, K**., Vaht, M., Mäestu, J., Veidebaum, T., Harro, J. (2015) Effect of tryptophan hydroxylase-2 gene polymorphism G-703T on personality in a population representative sample, *Progress in Neuro-Psychopharmacology & Biological Psychiatry,* 57, 31–35.

IV. Akkermann, K., **Hiio, K**., Villa, I., Harro, J. (2011). Food restriction leads to binge eating dependent upon the effect of the brain-derived neurotrophic factor Val66Met polymorphism. *Psychiatry Research* 185(1–2), 39–43.

Contribution of the author

Author of the present dissertation contributed to the publications as follows:

– for **Paper I**, conducting genotyping for the *BDNF* Val66Met polymorphism and all statistical analyses, writing the manuscript as the main author

– for **Paper II**, participating in ECPBHS methods development for the follow-up in 2008, formulating research hypothesis, conducting genotyping for the *COMT* Val158Met polymorphism and most of the statistical analyses, writing the manuscript as the main author

– for **Paper III**, participating in ECPBHS data collection for the follow-up in 2007, contributing in genotyping for the 5-HTTLPR polymorphism, formulating research hypothesis, conducting all statistical analysis and writing the manuscript as the main author

– for **Paper IV**, conducting genotyping for *BDNF* Val66Met polymorphism, contributing to writing the manuscript.

ABBREVIATIONS

5-HT	5-hydroxytryptamine; serotonin
5-HTT	serotonin transporter
5-HTTLPR	serotonin transporter linked polymorphic region
BDNF	brain-derived neurotrophic factor
CNS	central nervous system
COMT	catechol-O-methyltransferase
CSF	cerebrospinal fluid
DA	dopamine
DNA	deoxyribonucleic acid
EBBFI	Estonian Brief Big Five Inventory
ECPBHS	Estonian Children Personality, Behaviour and Health Study
EE.PIP-NEO	Estonian Personality Item Pool NEO
FFM	five-factor model
G × E	gene-by-environment interaction
G × G	gene-by-gene interaction
GWAS	genome wide association study
MAO	monoamine oxidase
MDD	major depressive disorder
NA	noradrenaline
NEO-PI-R	Revised NEO Personality Inventory
PCR	polymerase chain reaction
PFC	prefrontal cortex
S5	Short Five personality questionnaire
SNP	single nucleotide polymorphism
STAI	State – Trait Anxiety Inventory
TPH	tryptophan hydroxylase
TPH2	tryptophan hydroxylase-2
VNTR	variable number of tandem repeat

1. INTRODUCTION AND REVIEW OF LITERATURE

Untangling the origins of personality has been a popular subject of thought for many philosophers in ancient and modern times. The first known personality theories are dating back to ancient Greece, where a system of four humours was created to explain temperament and health through excess or shortage of four bodily fluids – blood, yellow bile, black bile and phlegm. Although this theory has been replaced by modern ones, questions about the biological basis of personality are still haunting many researchers in psychiatry and behavioural sciences. Despite the rapid developments in biotechnology, not much is known about the biological and genetic architecture of personality. Contemporarily, one of the central issues regards the role of personality traits, together with biological and genetic factors, underlying vulnerability to psychiatric disorders, e.g. depression and anxiety. In other words, why do some individuals suffer from mental illness but others do not? Answering this question would help to improve the understanding of human behaviour and would greatly contribute to the development of better treatment for psychiatric disorders.

1.1. Genetic vulnerability and personality traits as risk factors for depression

1.1.1. Depression

Depression is a common and seriously impairing disease, carrying the heaviest burden of disability among all other mental disorders worldwide (World Health Organization, 2008). Large scale epidemiologic studies have suggested that the prevalence of major depression can be as high as 7% and 16% for the 12-month and lifetime prevalence, respectively (Kessler et al., 2003, Wittchen et al., 2011). It is noteworthy that the prevalence differs drastically between genders, whereas the risk in women is nearly twice as large that in men (Gater et al., 1998, Kessler et al., 1993, Wittchen, 2011). Depression is characterized by a constellation of psychological, behavioural and physical symptoms (Cassano and Fava, 2002). These typically include lowered mood, anhedonia, lack of interest and motivation, feelings of guilt and worthlessness, reduced concentration and disturbances of sleep and appetite (DSM-IV, 1994, Cassano and Fava, 2002, ICD-10, 1992). Depression symptoms are to some extent overlapping with anxiety disorders and indeed both, depressive and anxiety disorders, often coexist in the same patient (Gorman, 1996). Although the first episodes of depression often occur in adulthood (Kessler et al., 2007), the proportion of early onset in childhood and adolescence is substantial (Fava and Kendler, 2000). Full recovery is difficult to achieve as most patients experience multiple relapses, and up to 25% of them suffer from a chronic and recurrent

course (Mueller and Leon, 1996). Considering the deteriorated quality of life for the patients, high prevalence of the disorder and the high chance of recurrences, depression is a significant contributor to the global burden of disease (Gustavsson et al., 2011, Murray and Lopez, 1997, Wittchen, 2011), as measured e.g. in Disability-Adjusted Life Years, which express the number of years of healthy life lost due to poor health, disability or premature death.

The etiology and biological mechanisms of the disorder remain poorly understood. For decades, the classic monoamine hypothesis has played a dominant role in antidepressant drug development. This theory emerged with the accidental discovery of the antidepressant properties of monoamine oxidase inhibitors (MAOIs), the prototype originally designed for treatment of tuberculosis, and tricyclic antidepressants (TCAs), the prototype originally designed as an antipsychotic, in the 1950s. The initial monoamine hypothesis associated low levels of extracellular monoamine neurotransmitters, serotonin (5-HT) and noradrenaline (NA), with depression (Bunney and Davis, 1965, Coppen, 1967, Schildkraut, 1965) and further led to the development of modern antidepressant drugs, e.g. the selective serotonin reuptake inhibitors (SSRIs). As new evidence has emerged about the complexity of pathophysiological mechanisms of depression, this theory has been advanced to more comprehensive models of chemical imbalance of the brain (Harro and Oreland, 2001), which emphasize, in addition to low levels of all monoamine neurotransmitters, the stepwise development of complex alternative changes in brain circuitries as depression develops. Further, the deteriorating effects of stress and depression on adult neurogenesis in hippocampus, and the ameliorating and reversing actions of antidepressants to these effects, have led to the neurogenic hypothesis (Duman and Monteggia, 2006, Villanueva, 2013, Warner-Schmidt and Duman, 2006), and recently complex neural plasticity theories of depression have been advanced (Wainwright and Galea, 2013).

The neurobiological mechanisms of depression are yet to be specified, but large scale epidemiological studies have identified several risk factors for depression susceptibility. Gender, stressful life events, adverse childhood experiences and certain personality traits are standing out with the largest evidence base and highest probability for causal link with developing depression (Fava and Kendler, 2000).

1.1.2. Vulnerability factors of depression

The vulnerability – stress model (also known as the diathesis – stress model) has often been used to explain the development of psychopathology. In the context of depression, vulnerability is a predispositional factor, or factors, which makes possible a disordered mental state (Ingram and Luxton, 2005). A person's predisposition combined with stress from life experiences could elicit depressive states that individuals without vulnerability do not develop. Regarding possible vulnerability factors, substantial amount of existing

evidence highlights genetic predisposition and negative emotionality as predictors of depression (Kendler et al., 2006, Kendler et al., 1993, Sullivan et al., 2000).

During lifetime, people can experience extreme stress from various life events and everyday problems are certainly of different nature for children, adolescents and adults. In childhood, the list of potential environmental stressors includes parental abuse, neglect, poor parent-child relationships, parental discord and divorce, whereas in adulthood, job loss, major health problems, marital difficulties and loss of a close personal relationship are all linked with a substantial increase in risk for the onset of depression (Fava and Kendler, 2000, Kendler et al., 2002). The presence of predispositional vulnerability, e.g. genetic and personality factors, increases the risk of developing depression when experiencing stress from the environment. However, it is not known how exactly the stressors lead from predisposition to depression.

1.1.2.1. Genetic vulnerability

Depression often runs in families. This notion is supported by a bulk of family studies, which have reported up to a 3-fold increased risk for depression in the first-degree relatives of probands with depression versus the general population (for a review and meta-analysis see Sullivan, 2000). One of the excellent methods of ascertaining the environmental and genetic influence are twin studies, which enable to "control" for genetic base as monozygotic twins who are genetically almost identical can be contrasted to dizygotic twins, who share half of their genes. According to some twin studies, the heritability of depression could be as high as 37% to 50% (Kendler et al., 2001, Kendler and Prescott, 1999, McGuffin et al., 1996, Sullivan, 2000). However, estimates of gross heritability alone do not give information about the genetic architecture of a disorder. This has led researchers to search for gene variants and genetic markers responsible for development of depression and associated phenotypes.

Depression is a heterogeneous and multi-faceted disease with most probably a very complex genetic architecture, with many contributing gene variants with a small effect size at the population level (Lohoff, 2010). A hypothesis-based candidate gene approach is one of the most widely used methods in psychiatric genetics, whereas in depression-related research, the candidate gene association studies have mainly been led by the classic monoamine hypothesis, but also the more recent neural plasticity theories (Levinson, 2006). Several functional polymorphisms, especially in the loci encoding the proteins of the 5-HT system, have repeatedly been associated with mood disorders or relevant traits, but as a rule these findings have not been consistently replicated (for reviews see: Levinson, 2006, Lohoff, 2010). Association of a few candidate gene variants with depression has survived meta-analysis, but even in these cases the population-level effect size is very small. Low statistical power and inadequacies in study design, as well as unknown functional relevance of tested single

nucleotide polymorphisms (SNPs) are considered among the main limitations of these studies (Hattersley and McCarthy, 2005, Lohoff, 2010).

A limitation of the candidate gene approach itself is that some *a priori* knowledge about the biological mechanisms of investigated trait is required to identify possibly relevant genes, which for depression, however, largely still remain to be understood. With the rapid developments in biotechnology, it is now possible to examine simultaneously the association of millions of common gene variants with health-related traits and hence great expectations have arisen also regarding unraveling the genetic architecture of depression. Genome-wide association studies (GWAS) have gained a lot of attention as a method for detecting specific genetic loci related to the etiology of a disease. GWAS are hypothesis free and new candidates can be scanned from the entire DNA structure. Indeed, some successful GWAS reports have been made (Hindorff et al., 2009), but a recent mega-analysis of GWA studies in 18 759 subjects failed to identify any specific loci which could play a role in increased (or decreased) risk of developing depression (Sullivan et al., 2013). There may be a number of reasons for the very limited success with GWAS, as discussed by the authors. For example, suboptimal or heterogeneous phenotype, divergent genetic architecture of MDD and insufficient power due to too small sample size were some of the highlighted issues. With the large-scale scans of hundreds of thousands SNPs on complex diseases with probably many small-effect genetic variants, there is a high chance of Type I errors which requires stringent multiple correction methods (usually Bonferroni correction). However, correction for multiple testing comes with a high price, as small genotype effects are likely to be considered insignificant (Williams and Haines, 2011). In addition, as GWA studies have originally focused on single-locus testing, statistical methods for reliable detection of more complex gene × gene (G × G) and gene × environment (G × E) interactions are currently under development and new approaches have only recently began to emerge (Gauderman et al., 2013, Hu et al., 2014). Conclusively, in spite of major advantages, the GWAS holds several limitations and therefore the hypothesis based candidate gene approach remains as a useful method in order to provide new insight in the genetic mechanisms underlying depression vulnerability. Any signal picked up by GWAS would anyway need further confirmation while probably using the candidate gene approach.

1.1.2.2. Personality traits

Of the personality traits, accumulating evidence has pointed out high Neuroticism as a considerable risk factor for developing depression (Clark et al., 1994, Enns and Cox, 1997, Kendler, 1993). Neuroticism was first defined by H. J. Eysenck as a stable personality trait that is perceived as a continuum ranging from the extremely stable to the extremely unstable, poorly integrated and neurotic personality type (Eysenck and Prell, 1951). It is also characterized

by dysphoria, anxiety, tension and emotional reactivity (e.g. Costa and McCrae, 1985). Neuroticism is one of the five-factor model (FFM) (i.e. Big Five) personality traits, which is a widely accepted set of five broad factors describing human personality, consisting of Neuroticism, Extraversion, Openness to Experience, Agreeableness and Conscientiousness (Costa and McCrae, 1992, Digman, 1990, Goldberg, 1993, John and Srivastava, 1999). The other four Big Five domains, apart from Neuroticism, are conceptualized as follows: Extraversion – an inclination to feel positive emotions, be energetic, talkative and outgoing; Openness to Experience – a tendency to be adventurous, curious, inventive and novelty seeking; Agreeableness – a predisposition to be compassionate, friendly, cooperative and helpful; Conscientiousness – an inclination to self-discipline, efficiency, dutifulness and personal organization (Costa and McCrae, 1992). All of the broad dimensions of FFM can be decomposed into six lower-order subscales (Goldberg, 1999), which are presented in Table 1.

Table 1. Five-factor model broad dimensions and their six subscales according to the International Personality Item Pool (IPIP) (Goldberg, 1999).

Neuroticism	**Extraversion**	**Openness to Experience**	**Agree-ableness**	**Conscien-tiousness**
Anxiety	Friendliness	Imagination	Trust	Self-efficacy
Anger	Gregariousness	Artistic interests	Morality	Orderliness
Depression	Assertiveness	Emotionality	Altruism	Dutifulness
Self-consciousness	Activity level	Adventurousness	Cooperation	Achievement-striving
Immoderation	Excitement-seeking	Intellect	Modesty	Self-discipline
Vulnerability	Cheerfulness	Liberalism	Sympathy	Cautiousness

The FFM personality traits emerged from the lexical approach to personality, originally formulated by Klages (1932), which states that the most important personality characteristics in people's lives will be encoded into their language, and more important traits are more likely to be expressed by a single word (Goldberg, 1993, John et al., 1988). Led by this theory, several independent researchers tried to identify the core personality factors, and after decades of such efforts, it became clear that similar five-factor structures were repeatedly found in distinct samples (Digman, 1990, Goldberg, 1993, John and Srivastava, 1999). These findings were supported by already existing personality constructs that had been developed for the personality assessments in clinical context. As mentioned above, H. J. Eysenck (1947) was the first to identify Neuroticism,

but he had also defined Extraversion as another broad personality dimension with a great importance in psychopathology, and he provided the Eysenck Personality Questionnaire (EPQ) as an assessment instrument (Eysenck, 1998, Eysenck and Eysenck, 1975). Merging of the lexical and clinical questionnaire-based traditions led to the formation of contemporary five-factor model of personality (e.g. McCrae and Costa, 1996, McCrae and John, 1992). In addition, with the development of the NEO Personality Inventory (NEO-PI) and its revised version NEO-PI-R, which measures all five Big Five main domains (Costa and McCrae, 1985, Costa and McCrae, 1992), a common standard in the personality assessment was created. The NEO-PI-R has gained notable success as the FFM-based personality inventories are widely used instruments for personality assessments by many researchers worldwide.

The validity of the FFM, assessed with the NEO-PI-R, has been extensively studied and large amount of evidence support the convergent and discriminant validity across self, peer and spouse ratings (McCrae and Costa Jr, 1989, McCrae and Costa Jr, 2004, Riemann et al., 1997). While the FFM traits are considered to be rather stable across adult life, some changes have been reported to occur during lifetime (Costa et al., 2000, Costa and McCrae, 1988, Roberts and DelVecchio, 2000). Although the FFM personality traits were derived from English, the same five-factor structure has been found in other languages and cultures (McCrae and Costa Jr, 1997, McCrae and Terracciano, 2005). These results suggest the universal nature of the FFM, which supports its use in investigation of possible underlying genetic factors. Indeed, based on twin studies, the heritability of FFM personality traits have been estimated to be between 40% to 60% (Jang et al., 1996, Jang et al., 1998), ranging from 0.41 to 0.49 for Neuroticism, 0.50 to 0.53 for Extraversion, 0.48 to 0.61 for Openness to Experience, 0.41 to 0.48 for Agreeableness and 0.44 to 0.49 for Conscientiousness (overview in Hare et al., 2012). The remaining variability is considered to represent the effects of non-shared environment, but probably also includes gene × environment interactions, measurement errors and chance factors in development (Bouchard and Loehlin, 2001). Interestingly, shared environment has only little or no effect (Bouchard and Loehlin, 2001, Jang, 1996).

Given the well-established notion of Neuroticism's role in depression etiology, a common genetic ground would be expected. Indeed, 55% of the estimated genetic risk of MDD is found to be shared with Neuroticism (Kendler, 1993). But in addition to Neuroticism, other personality traits are also associated with greater susceptibility for depression. For example, MDD has been predicted by low Extraversion (Enns and Cox, 1997, Fanous et al., 2007) and low Conscientiousness (Kendler and Myers, 2010, Kotov et al., 2010, Weiss et al., 2009).

Naturally personality traits also predict other psychiatric conditions and health-related behaviours. There is a wide evidence base for high Neuroticism to be associated with the development of anxiety disorders (Bienvenu et al.,

2004, Hettema et al., 2006) and together with low Conscientiousness it seems to contribute to substance abuse and dependence (Terracciano and Costa, 2004, Terracciano et al., 2008). Certain personality profiles are typical for personality disorders (Samuel and Widiger, 2008). Other studies point at the association of personality traits with beneficial behavioural endpoints: e.g. on the role of high Agreeableness, Conscientiousness and Openness to Experience in educational attainment (Poropat, 2009), high Extraversion and Conscientiousness in workplace performance (Thoresen et al., 2004) and low Neuroticism but high Extraversion and Conscientiousness in regular physical activity (De Moor et al., 2006, Rhodes and Smith, 2006).

To be noted, in the literature, negative emotionality is also measured with personality dimensions in other instruments, e.g. Harm Avoidance (HA) of the Cloninger's Tridimensional Personality Questionnaire (TPQ) and its newer, extended version, Temperament and Character Inventory (TCI) (Cloninger et al., 1993). Harm Avoidance is another personality trait often associated with depression and similarly to Neuroticism, HA is described as a trait of anxiety and pessimism (Cloninger et al., 2006). Indeed, Neuroticism and HA are found to be considerably overlapping, but not identical (De Fruyt et al., 2000). Differences exist in definitions of major domains by their subscales: Neuroticism is formed by six subscales of Anxiety, Anger, Depression, Self-consciousness, Immoderation and Vulnerability, however Harm Avoidance is composed of four subscales of Worry, Fear of Uncertainty, Shyness, and Fatigability (Schinka et al., 2004).

1.2. Candidate genes for negative emotionality

A genetic predisposition to vulnerability to stress, together with early exposure to stressful life events in critical stages of development, may affect neural development and result in a neurobiological phenotype which is reactive to stress in a way that may increase the risk of an individual to develop depression (Barlow et al., 2014, Lesch, 2004). Given the high probability of common genetic factors predisposing to both depressive symptoms and Neuroticism (Kendler, 1993), many efforts have been made by researchers to identify specific genetic markers responsible for personality traits, however, only few candidates have survived the replications. Although large-scale GWA studies have initially identified several loci related to personality traits, replication attempts so far have not been successful and it has been proven difficult to find reliable associations between genetic markers and personality traits (Bae et al., 2013, de Moor et al., 2012, Terracciano et al., 2011, Terracciano et al., 2010a). This, again, has been attributed to the complex genetic architecture of phenotypically broad traits, where probably many relevant genetic factors have an influence, each of them explaining only a small part of the phenotype variation. With the GWAS limitations like reaching sufficient power, and difficulties of

detecting genotype interaction effects with other genes and environmental factors (for a review see: Montag and Reuter, 2014), the results from candidate gene studies could again provide useful insights into the molecular mechanisms of depression and related personality traits.

As discussed above, the search for candidate genes for depression and negative emotionality is mainly led by the prevailing theories for depression, that is, the chemical imbalance and the neurogenic hypothesis. Therefore genes encoding key proteins of the 5-HT and dopamine (DA) systems, and neurotrophins have gained much of attention.

1.2.1. Serotonergic system

Phylogenetically, the serotonergic system is one of the oldest neurotransmitter systems in the central nervous system (CNS) (Tecott, 2007). It is involved in the regulation of various physiological processes, for example mood, appetite, sleep and memory. Serotonin is synthesized from the dietary precursor, amino acid tryptophan, which is converted to 5-hydroxytryptophan by the enzyme tryptophan hydroxylase (TPH), followed by decarboxylation by aromatic L-amino acid decarboxylase (DOPA decarboxylase) to 5-hydroxytryptamine (5-HT) (Walther and Bader, 2003). Interestingly, there are two TPH isoforms: TPH1 and TPH2, whereas TPH2 is exclusively in the brain and TPH1 is mostly found in the periphery (Walther et al., 2003). Serotonergic perikarya are located in the brainstem raphe nuclei and innervate the large majority of the CNS regions (Dahlström and Fuxe, 1964, Jacobs and Azmitia, 1992). Serotonin is released, by exocytosis, into the synaptic cleft between pre- and postsynaptic neurons and it activates serotonin receptors, which mediate both excitatory and inhibitory neurotransmission (Barnes and Sharp, 1999). The majority of the fourteen subtypes of 5-HT receptors are G-protein-coupled receptors, the exception being 5-HT_3, which is a ligand-gated cation channel. In the synapse, the action of 5-HT is throughout the CNS terminated primarily by the membrane-bound 5-HT transporter (5-HTT) molecules located on the presynaptic neuron, which regulate the synaptic 5-HT levels by re-uptake. Blocking some of the 5-HT re-uptake terminals, and hence, increasing the synaptic 5-HT levels, is the action mechanism for the most commonly used antidepressants, SSRIs (Hyttel, 1994), and also part of the mechanism of action of several other antidepressant groups such as the TCAs and SNRIs. 5-HT is primarily metabolized by monoamine oxidases (MAO), preferentially by the isoenzyme referred to by type A (Shih et al., 1999). MAO catalyses the oxidative deamination of 5-HT, which is followed by oxidation to the stable metabolite, 5-hydroxyindoleacetic acid (5-HIAA).

1.2.1.1. Serotonin in depression and related traits

The initial version of the monoamine hypothesis proposed the low levels of serotonin and noradrenaline in the synaptic clefts to form the basis of depression (Bunney and Davis, 1965, Coppen, 1967, Schildkraut, 1965). Because of the decades-long emphasis on this hypothesis, the key proteins of the 5-HT system have been the most studied amongst all neurotransmitter systems regarding the possible association with both depression and related personality traits. Indeed, there is no possibility to measure 5-HT release in the brain directly except after neurosurgery, and while positron emission tomography would allow indirect assessment as does pharmaco-fMRI provide some clues, most of the evidence must focus on proteins controlling the levels of 5-HT and mediating its action. A large amount of indirect evidence does support the role of 5-HT in depression. Historically, much interest was devoted to the lower levels of the 5-HT metabolite 5-HIAA in cerebrospinal fluid (CSF) of suicide attempters with major depression (Mann et al., 1996, Placidi et al., 2001, Traskman et al., 1981), but this has more recently been attributed more specifically to impulsivity associated with self-destructive behaviour (Harro and Oreland, 2001). In suicide victims, the serotonin transporter availability is decreased in post-mortem amygdala and 5-HT_{2A} receptor binding sites are increased in prefrontal cortex (PFC) and amygdala (Hrdina et al., 1993). Additionally, in the raphe nuclei of depressed suicide victims, increased levels of TPH2 and TPH2 protein per neuron have been found, which is suggested to be an adaptive response to functional serotonin deficiency in projection areas (Bach-Mizrachi et al., 2008). Also tryptophan depletion (TD), a paradigm for mood response to serotonin depletion achieved by dietary manipulations, induces depressive symptoms in some remitted depressive patients and healthy subjects (Smith et al., 1997, Young et al., 1985) and reverses antidepressant response (Delgado et al., 1999).

Serotonin transporter is a key protein in the regulation of synaptic 5-HT and therefore genetic variations in the 5-HTT gene have gained elevated attention in depression-related research. Probably the most studied psychogenetic factor is the variable number of tandem repeats (VNTR) polymorphism in the 5-HTT gene (*SLC6A4*) promoter region, the 5-HTTLPR. This polymorphism has a long allele with 16 repeats (L) and a short allele with 14 repeats (S), whereas carrying the S-allele results in lower transcriptional activity (Heils et al., 1995, Lesch et al., 1996). The S-allele can increase the risk for depression (Clarke et al., 2010), but these associations mostly emerge when stressful environmental factors are taken into account (Caspi et al., 2003, Kaufman et al., 2006, Sjöberg et al., 2006). In addition, the S-allele is also associated with suicidal behaviour (for a review see: Gonda et al., 2011). Consistently, the S-allele carriers have been reported to present heightened amygdala response to stimuli with negative affective valence (a review by Munafo et al., 2008), which is often found in depressed patients (Suslow et al., 2010). Lesch and colleagues (1996) originally found associations between the S-allele and negative emotionality (Lesch,

1996), including Neuroticism, but the results in replication studies have been inconsistent (see meta-analyses by Munafò et al., 2009, Schinka, 2004, Sen et al., 2004). One of the possible confounders is the choice of personality measurement instruments. A meta-analysis revealed that the association between negative emotionality and the S-allele of 5-HTTLPR has been most evident with FFM Neuroticism, in contrast to Eysenck's Neuroticism or the Harm Avoidance of the TCI (Munafò, 2009).

Tryptophan hydroxylase is the rate-limiting enzyme in the synthesis of 5-HT and hence another protein that is universally important for 5-HT-ergic neurotransmission throughout the CNS. The brain-specific isoform, TPH2, is encoded by the *TPH2* gene, which has hence become a candidate gene for a wide spectrum of psychiatric conditions (Waider et al., 2010). In mutant mice with genetic inactivation of *TPH2* function a number of phenotypic changes, such as growth retardation, late-onset obesity, enhanced conditioned fear response, increased aggression and depression-like behavior have been described (Lesch et al., 2013). In humans, a potentially functional single nucleotide polymorphism G-703T (rs4570625) in the promoter region of the *TPH2* gene has been described (Chen et al., 2008, Lin et al., 2007, but see Scheuch et al., 2007). Some reports have suggested that the T-allele carriers of the *TPH2* G-703T variation are more vulnerable to psychiatric disorders related to emotional dysregulation, such as personality disorders (Gutknecht et al., 2007) and depression (Mandelli et al., 2012). According to a recent meta-analysis of several variations in the *TPH2* gene, the G-703T polymorphism had the strongest link with major depressive disorder (MDD), the T-allele increasing the vulnerability (Gao et al., 2012). This is consistent with the brain imaging studies using functional magnetic resonance (fMRI), which have reported higher amygdala reactivity in face-processing tasks for T-allele carriers (Brown et al., 2005, Canli et al., 2005). In addition, the *TPH2* G-703T polymorphism has been implicated in other phenotypes that are possibly associated with emotional instability, e.g. low executive cognitive control (Baehne et al., 2009, Reuter et al., 2007b, Strobel et al., 2007), attention deficit hyperactivity disorder (ADHD) (Walitza et al., 2005) and obsessive-compulsive disorder (OCD) (Mössner et al., 2006). All this evidence makes *TPH2* and this particular promoter polymorphism a strong candidate for shaping inter-individual differences in anxiety-related personality traits. However, surprisingly little direct evidence is available in this regard. Of the few studies published to date, Gutknecht and colleagues (2007) found associations of a *TPH2* haplotype, including the G-703T variation's G-allele, with increased TPQ/TCI Harm Avoidance and FFM Neuroticism scores. Lower HA scores have been reported for T/T homozygotes (Reuter et al., 2007a). In a number of studies with relatively small sample sizes, however, no association was found with Neuroticism (Canli, 2005, Mandelli, 2012, Strobel, 2007).

1.2.2. Dopaminergic system

The best known neural pathways emerging from dopaminergic cells in the mammalian brain project either from ventral tegmental area (VTA) (mesolimbic/mesocortical pathway) or substantia nigra (nigrostriatal pathway) or are intra-regional (tuberoinfundibular pathway in hypothalamus). The mesolimbic/mesocortical pathway, which innervates the limbic system and frontal cortex, is crucial in behaviour aiming towards natural rewards, such as food, sex and social interaction, and also in drug addiction as well as depression (Koob and Le Moal, 2001, Nestler and Carlezon Jr, 2006, Wise, 1998).

Dopamine (DA) is synthesized in the cytoplasm from the amino acid tyrosine. The rate-limiting enzyme in dopamine synthesis, tyrosine hydroxylase, converts tyrosine to 3,4-dihydroxy-l-phenylalanine (L-DOPA). This is followed by the enzymatic activity of DOPA decarboxylase, catalyzing the conversion of L-DOPA to dopamine. The effects of DA are exerted through action on five dopamine receptor subtypes (D_1-D_5), which are all G-protein coupled receptors. In basal ganglia, the DA signal is terminated by the dopamine transporter (DAT), however in the PFC the DA reuptake is mediated by noradrenaline transporter (NAT) because of its much higher abundance there. The reuptake is followed by the degradation of DA by MAO and catechol-O-methyltransferase (COMT) to dihydroxyphenylacetic acid (DOPAC) and homovanillic acid (HVA) (Dunlop and Nemeroff, 2007, Molinoff and Axelrod, 1971).

1.2.2.1. Dopamine in depression and related traits

Dopamine is known by its role in the regulation of motivation (e.g. Depue and Collins, 1999, Ikemoto and Panksepp, 1999). As low motivation, anhedonia and decreased energy levels are common symptoms in depressive patients, the mesolimbic/mesocortical system is proposed to contribute to the patho-physiology of depression (Nestler and Carlezon Jr, 2006). Also animal models of depression imply the role of mesolimbic DA system function, whereas chronic antidepressant treatment acts to enhance DA neurotransmission in these brain regions (Willner, 1997). In depressed patients, lower levels of CSF HVA as compared to controls have been repeatedly reported (Goodwin et al., 1973, Mendels et al., 1972, Roy et al., 1989). The possible role of DA system in depression is also implicated by the co-occurrence of depression and Parkinson's disease, possibly mediated by dysfunction in mesocortical/ prefrontal reward, motivational, and stress-response systems (Cummings, 1992). The physiological mechanisms underlying reduced dopamine signaling in depression are not completely understood, however such a reduction could result from either diminished DA release from presynaptic neurons or impaired postsynaptic signal transduction, either due to changes in receptor number or function and/or altered intracellular signal processing (Dunlop and Nemeroff, 2007).

Catechol-O-methyltransferase is a major enzyme in the metabolic pathway of catecholamines that contributes to catabolism of various bioactive molecules throughout the organism and has a particularly important role in the prefrontal cortex (PFC) for degrading dopamine (Meyer-Lindenberg and Weinberger, 2006, Tunbridge et al., 2004). COMT is synthesized in two forms from the same gene – the soluble COMT-S and membrane-bound MB-COMT, whereas the MB-COMT is predominant in the brain (Männistö and Kaakkola, 1999).

A functional SNP in the *COMT* gene results in a methionine (Met) to valine (Val) substitution in the position 158 (*COMT* Val158Met) and impacts the activity of COMT enzyme. The Met form of the COMT enzyme is 3–4 fold less active and therefore results in increased levels of synaptic dopamine in the PFC (Chen et al., 2004a, Weinshilboum et al., 1999). The low activity Met-allele has been associated with enhanced cognitive functions. Carrying one or two copies of the Met-allele appears to be beneficial in working memory and attentional tasks (Barnett et al., 2008, Goldman et al., 2009, Mier et al., 2010, Savitz et al., 2006). However, the results of studies on the association of this genotype with depression and with anxiety disorders are very contradictory indeed. Some studies have reported increased corticolimbic responses to emotional stimuli for Met-allele carriers (Drabant et al., 2006, Smolka et al., 2005), but others show higher amygdala reactivity in Val-allele carriers (Domschke et al., 2012, Kempton et al., 2009, Lelli-Chiesa et al., 2011). Moreover, some have found the Met-allele to be associated with increased susceptibility to stress, anxiety and depression (Eley et al., 2003, Enoch et al., 2003, Stein et al., 2005), but on the contrary, others have identified the Val-allele as promoting increased susceptibility to these phenotypes (Domschke et al., 2004, Drury et al., 2010, Hettema et al., 2008, Massat et al., 2004, McGrath et al., 2004, Rothe et al., 2006). In addition, a number of reports fail to find any associations with depression or anxiety (Bækken et al., 2008, Frisch et al., 1999, Kunugi et al., 1997, Ohara et al., 1998, Serretti et al., 2003, Wray et al., 2008).

Similarily, the results on the effect of *COMT* Val158Met on negative emotionality are far from clear. While several studies show no significant associations with personality (Henderson et al., 2000, Ishii et al., 2007, Kang et al., 2010, Light et al., 2007, Urata et al., 2007), other authors have reported Met homozygotes to have lower Extraversion, higher Neuroticism (Eley, 2003, Hoth et al., 2006, Reuter and Hennig, 2005, Stein, 2005) and higher Harm Avoidance scores (Enoch, 2003, Hashimoto et al., 2007). Interestingly, Harris et al. (2005) did not find any effect on Neuroticism or Extraversion, but described a trend toward heterozygotes scoring higher on Agreeableness and Conscientiousness scales. But subjects with the Val/Val genotype have also been found to score higher in Sensation Seeking (Lang et al., 2007), Novelty Seeking (Tsai et al., 2004b), Harm Avoidance (Kim et al., 2006), negative emotionality scales (Chen et al., 2011), and higher in Trait Anger and lower in Anger Control scales (Baud et al., 2007). However, most of these genotype effects have been present only in female subjects (Baud, 2007, Eley, 2003, Enoch, 2003, Kim, 2006, Lang, 2007,

Stein, 2005, Tsai, 2004b), which suggests major gender differences in the contribution of the *COMT* Val158Met genotype and possibly prefrontal dopamine to behaviour.

The large amount of inconsistent findings provides rationale to assume the presence of some confounding factors. For example, the samples under investigation are very heterogeneous by many aspects and hence may lead to contradictory results. To provide further clarification, the effects of *COMT* Val158Met should be studied in large, unbiased and ethnically homogeneous samples.

1.2.3. Growth factors, with focus on brain-derived neurotrophic factor

Brain-derived neurotrophic factor (BDNF) is a member of the neurotrophin family of growth factors, together with three other types of neurotrophins: nerve growth factor (NGF), neurotrophin-3 and neurotrophin-4. Their main function is to induce and support the differentiation, survival, development and function of neurons (Huang and Reichardt, 2001). BDNF is initially produced as a precursor molecule proBDNF, which is followed by proteolytic cleaving to mature BDNF (Lu, 2003). ProBDNF acts by binding to the receptor p75, whereas mature BDNF binds to its receptor tyrosine kinase TrkB (Chao and Bothwell, 2002). In the CNS, the role of BDNF is especially prominent in the hippocampus and cortex as an enhancer of synaptic plasticity and neuro-transmission (Croll et al., 1994, Lessmann et al., 1994, Levine et al., 1995, Marty et al., 1996, McAllister et al., 1999, Nawa et al., 1993, Poo, 2001). This effect is believed to be induced by the neuronal activity-dependent secretion of BDNF, a function distinct of other growth factors, which are secreted constitutively (Lu, 2003). The activity-dependent secretion of BDNF is crucial in hippocampus-dependent memory processes (Egan et al., 2003, Lu and Chow, 1999). The *BDNF* and *trkB* knockout mice exhibit severe deficits in memory and learning (Linnarsson et al., 1997, Minichiello et al., 1999).

1.2.3.1. BDNF in depression and related traits

A large body of evidence shows that stress and depression can lead to neuronal atrophy and cell loss in key limbic and associated brain regions implicated in depression, including amygdala, PFC and hippocampus, and altered expression of neurotrophic factors is found to have a functional significance in these processes (Duman and Monteggia, 2006, Manji et al., 2001, Villanueva, 2013). Brain imaging studies have reported decreased volumes in structures such as hippocampus and PFC in depressed patients (Drevets et al., 2008, Videbech and Ravnkilde, 2004). In addition, it is widely recognized that stress decreases and antidepressant treatment increases hippocampal neurogenesis (Warner-Schmidt and Duman, 2006). The importance of BDNF in depression

susceptibility has been highlighted, as decreased expression of BDNF contributes to the onset of depression and upregulation of BDNF plays a role in the actions of antidepressant treatment (Duman and Monteggia, 2006).

BDNF is coded by the *BDNF* gene, which includes a SNP Val66Met in the 5' pro-domain of the *BDNF* gene. An amino acid substitution of valine (Val) to methionine (Met) at codon 66 affects hippocampal function and memory processes (Egan, 2003, Hariri et al., 2003, Pezawas et al., 2004). The Val form of BDNF not only reaches the neurites better but also allows for better activity-dependent secretion of BDNF (Chen et al., 2004b). In a fMRI experiment, the Met-allele was associated with stronger amygdala reaction in response to emotional stimuli (Montag et al., 2008). In addition, Met-allele has also been reported to contribute to the onset of mood disorders (Kaufman, 2006, Kim et al., 2007, Verhagen et al., 2010), eating disorders (Ribases et al., 2003, Ribases et al., 2004), obsessive-compulsive disorder (Hall et al., 2003) and schizophrenia (Frustaci et al., 2008, Hünnerkopf et al., 2007, Sen et al., 2003). Studies on any eventual effect of the *BDNF* Val66Met polymorphism on personality traits have resulted in discordant findings. The Met-allele has been associated with lower Neuroticism (Frustaci, 2008, Hünnerkopf, 2007, Sen, 2003) and Extraversion (Itoh et al., 2004, Terracciano et al., 2010b), but others reported no association (Tochigi et al., 2006, Tsai et al., 2004a).

1.2.4. Gene × gene interactions

Because of the assumption that depression and personality traits have a complex genetic base, interactions between variants of different genes that encode proteins within neurobiological systems, and proteins of interacting systems, are expected. Indeed, the literature provides a large amount of relevant reports on genotype interactions, most of them concentrating on polymorphisms in genes encoding the proteins of the 5-HT system.

As probably the most investigated psychogenetic marker, 5-HTTLPR has been studied widely regarding possible gene × gene interaction effects on depression and related traits. Because 5-HTT and TPH2 are the two key proteins for regulation of neurotransmitter levels in the serotonin system, the interaction of the functional variants of corresponding genes in behavioural regulation is of obvious interest. To our knowledge, no report has been published on *TPH2* G-703T × 5-HTTLPR interaction effect on personality traits. Nevertheless, an additive effect of these two genotypes has been described in an emotional picture viewing task using event-related potentials (ERPs), and in cognitive-affective tasks with emotional and neutral facial expressions and word stimuli by fMRI (Canli et al., 2008; Herrmann et al., 2007). Carriers of the 5-HTTLPR short variant and the T-allele of *TPH2* exhibited the greatest degree of neural activation in these tasks. Recently, Hahn and colleagues (2013) have reported a positive correlation between connectivity of amygdala and hippocampus, and Gray's trait anxiety (BIS)

scores in individuals with presumably low synaptic 5-HT level. Low synaptic 5-HT subjects were defined in this study as *TPH2* G-allele homozygotes and 5-HTTLPR L_A-allele homozygotes. Interestingly, in the high 5-HT level group, comprising *TPH2* T-allele carriers with at least one 5-HTTLPR S or L_G-allele, a negative association was found instead (Hahn et al., 2013). These findings suggest such an interaction between the two genotypes that should have a reflection in the style of reaction to the environment, *i.e.,* personality.

As BDNF promotes the development and function of serotonergic neurons (Martinowich and Lu, 2008, Ren-Patterson et al., 2005), interactions of *BDNF* variants with genes affecting the serotonin system should be expected. Indeed, some studies have found interaction effects of 5-HTTLPR and *BDNF* Val66Met genotypes on depression and related phenotypes. It has been reported that the *SLC6A4* gene interacts with *BDNF* to impact amygdala and anterior cingulate cortex volume (Pezawas et al., 2008). Furthermore, an interaction effect of 5-HTTLPR and *BDNF* Val66Met and stressful life events has been shown on depression in children (Kaufman, 2006) and elders (Kim, 2007). In addition, it has been found that the *BDNF* gene moderates the association of 5-HTTLPR with biological stress responses in preschoolers (Dougherty et al., 2009) and the effect of 5-HTTLPR on worrying (Bredemeier et al., 2014). Of personality traits, Terraciano and colleagues (2010) reported a G × G interaction effect on personality: 5-HTTLPR L/L homozygotes scored lower on Neuroticism in the presence of *BDNF* Val variant, whereas they scored higher with the Met-allele.

Regardless of the large number of studies on gene associations with depression-related personality traits, the results have not led to a clear picture. There are most likely several reasons for limited replications. One of the main issues is the small effect size of the gene variants, which are of course expected for complex traits. Moreover, small sample sizes, high ethnic diversity and large varieties in the age and health status of the subjects have been highlighted as probable confounding factors in candidate gene studies (Chen, 2011). Therefore, leaving aside the widely used convenience samples, an ethnically homogeneous population representative sample with a longitudinal database would contribute greatly to the clarification of the ever-increasing amount of contradictory results. Furthermore, such a sample design would enable to assess the effect size for general population.

2. AIMS OF THE STUDY

Studies included in this dissertation were intended to explore how do common variants of neurotransmission-related genes, often linked to depression and negative emotionality, associate with personality traits in a large population representative sample.

More specifically,

- Does the *BDNF* Val66Met polymorphism have any effect on personality traits? (**Paper I**)
- Is *COMT* Val158Met polymorphism associated with personality traits? (**Paper II**)
- Is *TPH2* genotype affecting personality traits? (**Paper III**)
- Does any eventual association of *TPH2* and *BDNF* genotypes with personality interact with the 5-HTTLPR genotype? (**Papers I and III**)
- Are eventual associations of these functional gene variants with personality reflected in health-related and personality dependent behaviours, such as binge eating (**Paper IV**), educational attainment (**Paper II**) and depressiveness (**Unpublished data**)

3. MATERIALS AND METHODS

3.1. The sample

The sample consisted of the two age cohorts of the European Youth Heart Study that was conducted in Estonia in 1998/99 and subsequently incorporated into the longitudinal Estonian Children Personality Behaviour and Health Study (ECPBHS). It is an ethnically homogeneous sample of Caucasian participants and the rationale for sample formation and the procedure has previously been described (Harro et al., 2009, Harro et al., 2001, Laas et al., 2014, Tomson et al., 2011). Briefly, 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 (Cohort 1; younger cohort) and 9 (Cohort 2; older cohort) were invited to participate and written informed consent was received from 76% of the invited subjects and their parents. The total number of subjects in this sampling was 1176 (583 in Cohort 1, age 9.6 (SD = 0.5) years, 593 in Cohort 2, age of 15.4 (SD = 0.6) years). The follow-up studies for the younger cohort took place in 2004 (n = 483, age = 15.3 (SD = 0.5)) and 2007 (n = 453, age = 18.3 (SD = 0.5)); for older cohort, the follow-ups were in 2001 (n = 417, age = 18.3 (SD = 0.7)) and 2008 (n = 487, age = 24.7 (SD = 0.7)). Permission for the study was obtained from the Ethics Review Committee on Human Research of the University of Tartu. The study was conducted in accordance with the Declaration of Helsinki.

3.2. Measurements

3.2.1. Personality measurements

The five-factor model personality traits (**Papers I, II and III**) were measured by self-reports with the Estonian version of Revised NEO Personality Inventory (NEO-PI-R) (Kallasmaa et al., 2000), EE.PIP-NEO (Mõttus et al., 2006), which is a semantically simplified full-length version of NEO-PI-R, Short Five (S5) (Konstabel et al., 2011), which is a short inventory of five-factor personality, or Estonian Brief Big Five Inventory (EBBFI), which is a short and semantically simplified questionnaire (Harro, 2009, Laidra et al., 2006). All scales measure each of the FFM personality dimensions (Neuroticism, Extraversion, Openness to experience, Agreeableness and Conscientiousness), and their six subscales with the exception of EBBFI. All four instruments have been found to provide realistic and convergent assessment of personality according to the five-factor model (Konstabel, 2011, Laidra, 2006, Mõttus, 2006). Personality data were collected at age 15 (younger cohort: EE.PIP-NEO; older cohort: EBBFI), 18

(younger cohort: S5; older cohort: NEO-PI-R) and 25 (older cohort: EE.PIP-NEO). Data were standardized into z-scores for common analysis.

3.2.2. Psychiatric disorders

The Mini-International Neuropsychiatric Interview (M.I.N.I.5.0.0; Sheehan et al., 1998, Estonian version: Shlik et al., 1999) was used to screen for major psychiatric disorders at the age 25 (**Paper II**). Diagnostic assessment was carried out by experienced clinical psychologists.

3.2.3. Educational attainment

At the age 25, the participants were asked to report their current level of education, either as 1) primary; 2) secondary; 3) vocational; 4) incomplete higher; 5) higher education (**Paper II**). For the statistical analysis the level of education obtained was stratified in three levels: 1) primary; 2) secondary and vocational; 3) higher (including incomplete higher) education.

3.2.4. Socioeconomic status

The participants were asked to report their monthly income, as well as the monthly income of their household (**Paper II**). Also they were asked to assess the economic status of their household on a 5-point scale, ranging: 1 – we have huge difficulties in coping ….. 5 – we are coping very well. To assess the perceived socioeconomic status the participants were asked to rate themselves on a 10-step scale ranging: 1 – I feel repelled from society ……10 – I feel I belong to the most influential part of society.

3.2.5. Body weight regulation

Participants were asked whether they have tried to regulate their body weight (1. Yes, I have tried to increase my body weight, 2. No, I don't think it's necessary to regulate my body weight, 3. Yes, I have tried to decrease my body weight), and indicate which methods of the following they had been using: dieting (avoiding high-fat and/or high carbohydrate food), restriction of meal sizes, training, reduction in meal frequency, starvation (no food intake for at least 24 h), or any other methods not mentioned in the questionnaire (**Paper IV**).

3.2.6. Eating behaviour and attitudes

Two subscales of Eating Disorders Inventory-2 – Drive for Thinness and Bulimia – were used to assess eating behaviour and attitudes (EDI-2; Garner, 1991; Estonian versioon: Podar et al., 1999) (**Paper IV**). The Drive for

Thinness subscale measures concern and preoccupation with dieting and weight gain, the Bulimia subscale measures the tendency to think about and engage in episodes of binge eating. These subscales have been shown to be most directly related to eating-disordered behaviour (Hurley et al., 1990).

3.2.7. Depressiveness

Depressiveness was assessed during the second and third study wave using the self-report format of the Montgomery – Åsberg Depression Rating Scale (MÅDRS; Montgomery and Åsberg, 1979) or Beck Depression Inventory (BDI; Beck et al., 1961) (**Unpublished data**). Subjects of the younger cohort filled BDI at age 15 and MÅDRS at age 18; and subjects of the older cohort filled MÅDRS at ages 18 and 25.

3.2.8. Anxiety

Anxiety levels were measured with the Spielberger State Trait Anxiety Inventory (STAI; Spielberger, 1983) (**Unpublished data**). Anxiety data were collected from the younger cohort at ages 15 and 18; and from the older cohort at age 25.

3.2.9. Genotyping

3.2.9.1. 5-HTTLPR

DNA was extracted from venous blood with QIAamp DNA Midi kit (Qiagen, Hilden, Germany). The alleles at the 5-HTTLPR locus were amplified following protocols described by Paaver et. al (2007) (**Paper I**) and Tomson et al. (2011) (**Paper III**).

In **Paper I**, the alleles at the 5-HTTLPR locus were amplified from genomic DNA using PCR. 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 reaction were: 1× PCR buffer (Perkin Elmer, AmpliTaq Gold buffer II), 200 μM dNTP with 50% of dGTP replaced with 7 deaza-dGTP, 2 mM $MgCl_2$, 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, U.S.A.). All genotypes were manually checked on chromatograms to detect inconsistencies and where needed, amplified and scored a second time.

In **Paper III**, the 5-HTTLPR polymorphic region was amplified using the primers 5-HTTLPR-F: 5′-6FAM-ATG CCA GCA CCT AAC CCC TAA TGT-3′ and 5-HTTLPR-R: 5′-GGA CCG CAA GGT GGG CGG GA-3′. PCR reaction components and final concentration were as follows: 1 x of 5x HotFirepol BLEND with BSA 2.5 mM $MgCl_2$ (Solis Biodyne); 5% of DMSO; 1 x of 10x Solution S (Solis Biodyne); 380 µM each of the forward and reverse primers; 10–50 ng of template DNA. The amplification was conducted in a total volume of 20 µl. The touchdown PCR cycles were used as by Anchordoquy et al. (2003). The electrophoresis was made on ABI PRISM 3130XL genetic analyser (Applied Biosystems, USA) and the components used were: 1 µl PCR product, 10 µl Hi-Di formamide, 0.25 µl Liz 500 size standard. Genotypes were generated using ABI Gene-Mapper V 4.0 software.

3.2.9.2. *BDNF* Val66Met

BDNF Val66Met (SNP rs6265) genotyping was carried out by restriction analysis, and to eliminate any chances of false positive or false negative results, extra sequencing reactions were performed on 23% of the sample (**Papers I and IV**). No inconsistencies between the two methods occurred.

Amplification reactions were performed in a total volume of 20 µl with 10–50 ng of template DNA, using thermal cycler „Biometra UNO II". PCR reaction components and final concentration were as follows: 1:10 tartrazine buffer (750 mM Tris HCl, pH 8.8, 200 mM $(NH)_2SO_4$, 0.1% Triton x 100, 5% Ficoll 400, 10 mM tartrazine); 1.9 mM $MgCl_2$; 0.1 mM dNTP; 0.5 pmol/µl primer F 5'-ACT CTG GAG AGC GTG AAT-3'; 0.5 pmol/µl primer R 5'-ATA CTG TCA CAC ACG CTC-3'; 1.5U Taq DNA polymerase (FIREPol). To determine the possible contamination, a negative control was added to every experiment. The PCR cycling conditions consisted of an initial denaturation of 2 min at 95°C, followed by 37 cycles of 96°C for 20 s, 50°C for 15 s, 72°C for 40 s, and final extension 72°C for 6 min. PCR products were visualized on 2% agarose gel electrophoresis with ethidium bromide.

3.2.9.3. *COMT* Val158Met

COMT Val158Met polymorphism (rs4680) genotyping reactions were performed in a total volume of 20 µl with 10–50 ng of template DNA. The real-time polymerase chain reaction (RT-PCR) was performed with primers and fluorescent probes obtained from Applied Biosystems (Foster City, CA, USA) Custom TaqMan SNP Genotyping Assays. RT-PCR reaction components and final concentrations were as follows: 1:5 5xHOT FIREPol Probe qPCR Mix Plus (ROX) (SolisBiodyne) and 1:20 80xTaqMan Primers Probe (F 5' –CCCAGCGGATGGTGGAT –3'; R 5' –CAGGCATGCACACCTTGTC –3'; Reporter 1 –TTCGCTGGCATGAAG (VIC); Reporter 2 –TCGCTGGCGTGAAG (FAM)). Reactions were performed on the ABI 7500 Real-Time PCR system

(Applied Biosystems, USA) and the amplification procedure consisted of an initial denaturation step at 95°C for 15 min and 40 cycles of 95°C for 15 s and 60°C for 1 min. All reactions were carried out in duplicate and extra negative controls were added to each reaction plate.

3.2.9.4. *TPH2* G-703T

Genotyping for TPH2 G-703T (rs4570625) was performed on the Applied Biosystems ViiA™ 7 Real-Time PCR System using TaqMan® Pre-Designed SNP Genotyping Assay and Solis BioDyne 5x HOT FIREPol® Probe qPCR Mix Plus (ROX).

3.3. Statistical analysis

Owing to the small number of *BDNF* Val66Met Met homozygotes in our sample (n=19), the genotype was divided into two groups – Val homozygotes in one group (Val) and Met-allele carriers in another group (Met). All other genotypes (5-HTTLPR, *COMT* Val158Met, *TPH2* G-703T) were grouped based on their allelic variances. All genotype frequencies were found to be consistent with the Hardy-Weinberg equilibrium.

For statistical analyses, one-way and two-way analysis of variance or covariance (ANOVA or ANCOVA) were used to test the main effects on personality traits of all polymorphisms under investigation, and gene × gene interactions with the 5-HTTLPR polymorphism or interaction with sex. ANOVA was also used to test the associations between the test scores of eating behaviour and the *BDNF* Val66Met genotype. Mixed linear model analysis was carried out to test the interactions with age. Fisher's LSD was used for post-hoc comparisons and contrasts were calculated for significant model effects. To test for main effects of *COMT* Val158Met on education and psychiatric disorders the Pearson chi-square test was used. Mixed linear model analysis was carried out using the SPSS Statistics version 19. All other statistical analyses were carried out with STATISTICA 7.0.

4. RESULTS AND DISCUSSION

4.1. Associations of depression- and anxiety-related gene polymorphisms with personality

4.1.1. *BDNF* Val66Met polymorphism and personality traits (Paper I)

BDNF Val66Met polymorphisms was associated with Conscientiousness, whereas the Met-allele carriers scored significantly lower than Val-homozygotes ($F(1,807) = 4.32$, $p = 0.038$). The Met-allele carriers thus tend to be less organized, determined and cautious, but also more impulsive and spontaneous than the Val homozygotes. The deteriorating effect of the Met-allele was most evident with C1: Self-Efficacy and C2: Orderliness facets (Figure 1), which indicates that Met-allele carriers may have lower level of accomplishment, effectiveness and organization, compared to their peers.

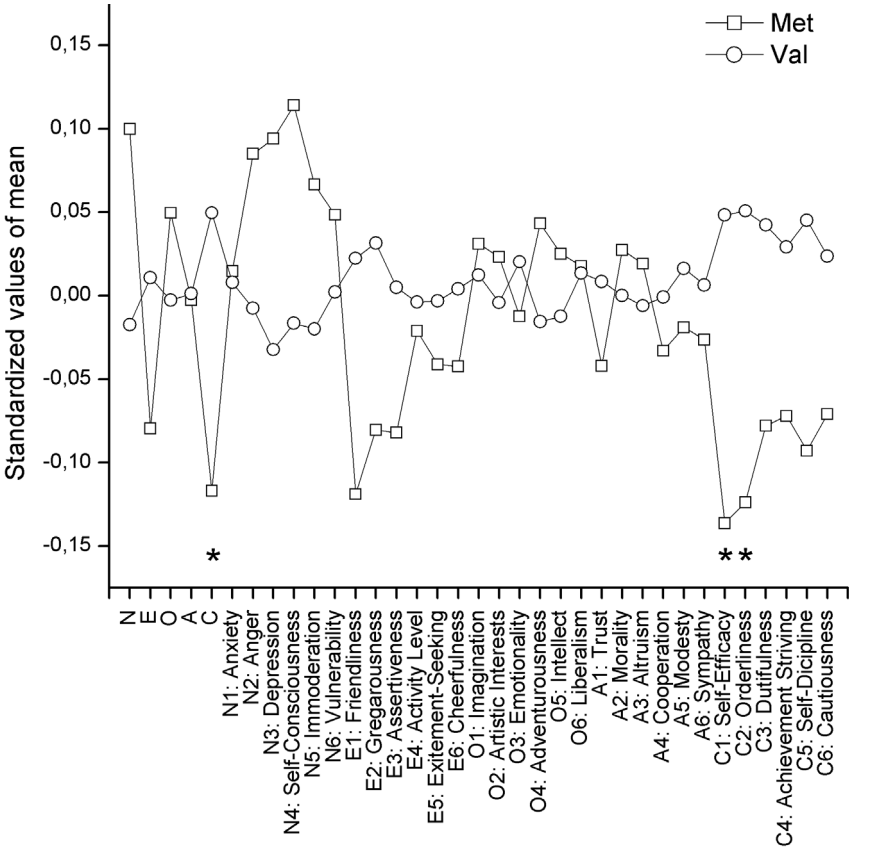

Figure 1. Personality profiles for *BDNF* Val homozygotes and Met-allele carriers. * – significant differences between Val homozygotes and Met-allele carriers.

Besides high Neuroticism, low Conscientiousness has repeatedly been found to increase depression risk (Kendler and Myers, 2010, Kotov, 2010). Health-related effects of Conscientiousness may arise from its influence on behaviours that may lead to poor health, e.g. substance use (Terracciano, 2008) or lack of physical exercise (Rhodes and Smith, 2006). Conscientiousness, as a trait for high orderliness, efficiency and self-discipline, is also related to prospective memory (Uttl et al., 2013). Indeed, to be conscientious, one has to be able to make and follow plans, which requires good memory performance. Given the importance of BDNF in memory processes (e.g. Egan, 2003), our findings may indicate that fundamental brain functions (i.e., personality and memory) have some overlaps in their genetic architecture. On the other hand, memory can contribute to the perception of Conscientiousness through remembering certain behaviours from the past, when completing the personality questionnaires.

Several previous studies have reported the Met-allele carriers to score lower on Neuroticism or Extraversion scales, however no association has previously been observed regarding Conscientiousness. There may be a number of reasons for this. The principles of sample formation may influence the variability of personality dimensions in the sample. The study of Sen and colleagues (Sen, 2003) that originally demonstrated the effect of Val66Met polymorphism on Neuroticism did not reveal any genotype effect on other FFM personality dimensions, including Conscientiousness. The sample they used was recruited from a blood pressure monitoring program targeted on families, and thus certainly not representative of the whole population. It is likely that their sample was relatively high in Conscientiousness, because this personality trait would facilitate family life and involvement in a long-term program targeted at health issues. In a small Japanese study which was on a sample of staff and students of a university, the results in fact reflected a non-significant trend towards lower Conscientiousness in Met carriers (Itoh, 2004). However, several studies have shown that high Conscientiousness can predict academic success (Noftle and Robins, 2007, O'Connor and Paunonen, 2007, Vedel, 2014). High school students are more conscientious and therefore more successful in their studies than their peers. When the sample is composed entirely out of college and university students, then it is already significantly biased towards higher Conscientiousness. Hence the dispersion of this trait might be too small, leading to false negative results.

The data of this study were collected from the second study wave, where the average age for the younger cohort was 15 and older cohort 18 years. As of writing this dissertation we have collected additional data from the third study wave, where the average age was 18 and 25 years for younger and older cohort, respectively, and this allows us to pool data of both cohorts age-wise at age 18. We failed to detect any significant *BDNF* Val66Met main effects on Conscientiousness, however, a tendency for a gene × sex interaction emerged ($F(1, 821) = 3.70$, $p = 0.055$). Male Met-allele carriers expressed a strong trend for lower Conscientiousness, compared to all other subjects. These results

support previous findings on gender specific effects of the *BDNF* Val66Met polymorphism on depression, whereas male Met-allele carriers show increased risk (for a meta-analysis see Verhagen, 2010). However, as the mean age of subjects included in the meta-analysis were higher compared to our sample (50.6 years for cases and 47.6 years for controls), this issue should be addressed again in the future in our longitudinal sample to assess possible age-dependent effects.

4.1.2. *COMT* Val158Met genotype and personality traits (Paper II)

The importance of dopamine in behaviour and psychopathology gives reason to examine the possible role of *COMT* Val158Met polymorphism on personality traits and their development on a large population representative sample, which we addressed in **Paper II**. We used the data of all three study waves on the older cohort of the ECPBHS sample, the participants having respectively been 15, 18 and 25 years old. Mixed linear modeling of these longitudinal dataset of general population revealed that in the five-factor model, *COMT* Val158Met does have an effect on personality traits, particularly on Neuroticism. Interestingly these effects became manifest by the time of young adulthood, observed at the present study at age 25, by which age women with the Val/Val genotype had developed higher Neuroticism (Figure 2). This made it irrational to examine the genotype effect on personality in the younger cohort of the ECPBHS until they will have been participated in the scheduled data collection wave at age 25. In addition, we found the effect of *COMT* genotype on Conscientiousness to increase with age. By the age of 25 female heterozygotes scored higher than both homozygote groups on the Conscientiousness scale. There was a tendency of low Conscientiousness being more evident in males, whereas high Neuroticism is manifested more in females. In population-representative samples, Neuroticism and Conscientiousness correlate negatively, and in the future, it seems worthwhile to examine whether subgroups of males and females have, dependent on *COMT* genotype, different perception of aspects of these traits.

Reported associations of gene variants affecting the activity of the dopamine system with personality traits have been inconsistent (Ebstein, 2006, Reif and Lesch, 2003) and so our findings also stand in contrast to several of the previous results regarding *COMT* Val158Met effect on personality traits (Eley, 2003, Hoth, 2006, Reuter and Hennig, 2005, Stein, 2005). As noted by Chen and colleagues (Chen, 2011), some of the reasons for inconsistent results in the studies with *COMT* genotype may be due to small sample sizes, high ethnic diversity and different age groups. Age-dependency of effects of functional gene variants on personality has previously been reported (Harro and Kiive, 2011, Harro, 2009, Laas, 2014). A twofold increase in COMT enzyme activity has been shown from post-birth to adulthood (Tunbridge et al., 2007) and this

may have an effect on the development of personality traits. Therefore, the developmental stage should be considered while comparing different studies on the association of genes and personality, and in elucidating the mediating neurobiological mechanisms.

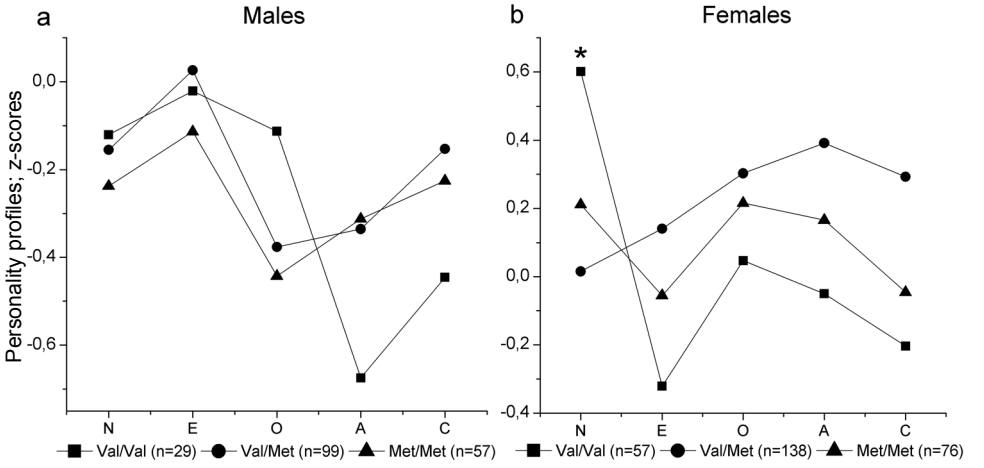

Figure 2. Personality profiles by genotype and gender at age 25; z-scores. *: $p < 0.05$ vs. all comparison groups. N: Neuroticism; E: Extraversion; O: Openness to experience; A: Agreeableness; C: Conscientiousness.

Of other personality traits, Conscientiousness, mostly associated with being organized, responsible and dependable, is the best predictor of mental health. Our results indicate that in addition to the increased Neuroticism by the age 25, Val homozygotes scored the lowest on Conscientiousness scale. Although Neuroticism is a strong predictor of stress and dysphoria the correlations between Neuroticism and different anxiety disorders vary (Watson et al., 2005), thus it would be reasonable to explore the association of *COMT* genotype in relation to different types of anxiety disorders with adequate sample size. Since the manifestation of mental disorders, including anxiety disorders and depression, are moderated by adverse life events and social support, it would be worthwhile to address these aspects in relation to *COMT* genotype as well. Nevertheless, excessive speculation should be avoided at this stage, as the results of this study should be considered exploratory because of the limitation of not correcting for multiple testing that makes replications on other samples mandatory before major conclusions can be drawn.

4.1.3. *TPH2* G-703T genotype and personality traits (Paper III)

Variations in the tryptophan hydroxylase gene, encoding for the rate-limiting enzyme in the 5-HT synthesis, may modulate the 5-HT system and therefore also behaviour. Hence, in **Paper III**, we aimed to study the effects of *TPH2* G-703T polymorphism on personality traits and their development in this large population-representative sample. We pooled the data of the younger and older cohorts age-wise, at age 15 (n = 742) and 18 (n = 834). We found that, indeed, the *TPH2* G-703T genotype is associated with personality traits of the five-factor model. At age 15, subjects with the T/T genotype scored considerably lower on Neuroticism and higher on Conscientiousness scale. Three years later, by the age of 18, the T/T homozygotes again scored the highest on Conscientiousness and also Extraversion, however the effect on Neuroticism was no longer significant (Figure 3). Indeed, the mixed linear model analysis revealed the age-dependent genotype effect on Neuroticism, whereas at age 15 the T/T homozygotes scored significantly higher compared to G-allele carriers, but by the age 18 they were more similar to other groups.

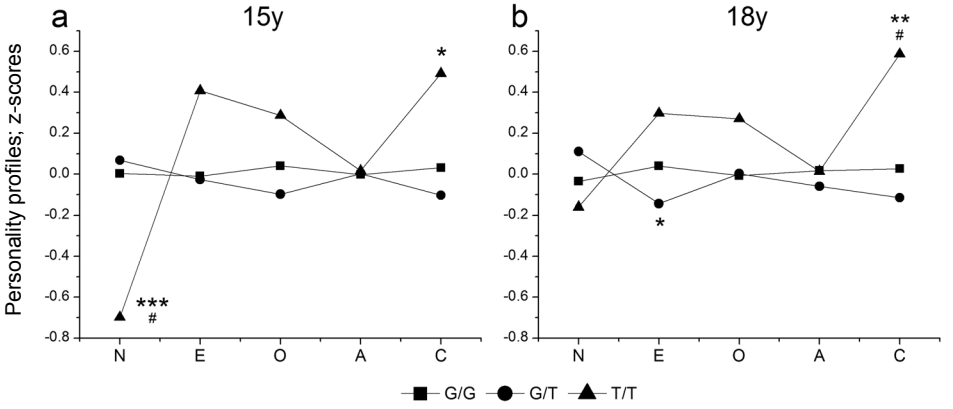

Figure 3. *TPH2* G-703T genotype and personality profiles at age 15 and 18. Data are presented as z-scores. * – $p < 0.05$ *vs.* all comparison groups; ** – $p < 0.001$ *vs.* G/T; *** – $p = 0.0001$ *vs.* G/T; # – $p < 0.001$ vs. G/G (Fisher's LSD). N: Neuroticism; E: Extraversion; O: Openness to experience; A: Agreeableness; C: Conscientiousness.

Our results are consistent with previous findings on higher negative emotionality in the G/G genotype that were based on Harm Avoidance scores (Reuter, 2007a). However, none of the previous studies had found G-703T main effect on Neuroticism, the negative emotionality scale of the FFM. Gutknecht and colleagues (2007) reported a haplotype association of *TPH2* G-703T with TPQ Harm Avoidance and FFM Neuroticism, in a sample of university students (n = 336). Strobel et al. (2007) have described a tendency of G/G homozygotes

scoring higher on Neuroticism, however, as pointed out by the authors, the sample size was small (n = 78). In a number of studies the T/T and G/T genotype groups have been combined and contrasted to G/G homozygotes, due to the small number of T/T homozygotes (e.g. Canli, 2005, Hahn et al., 2013, Strobel, 2007). However, some evidence has suggested that subjects with the T/T genotype could differ from the other genotype groups, e.g. they scored lower on HA scale (Reuter, 2007a), and this is consistent with the present data in a large population-representative sample. Interestingly, the G/T and G/G subjects had a very similar personality profile.

Because of the broad and comprehensive nature of the main domains, analyses on the facet level may lead to better prediction of behaviour (Paunonen and Ashton, 2001). We therefore further examined the *TPH2* G-703T effect on the subscales of Conscientiousness at age 18, when the association was the strongest. Amongst the six subscales of Conscientiousness domain our results show the strongest genotype association with Orderliness and Self-Discipline, and the weakest with Cautiousness. Speculatively, this may have implications to a potential link between serotonergic system and locus of control. The present study also suggests that the *TPH2* G-703T genotype association with personality should not be expected in studies with small number of participants unless the sample is biased.

4.1.4. Moderation by the 5-HTTLPR genotype of the gene × personality associations (Papers I and III)

4.1.4.1. *BDNF* Val66Met × 5-HTTLPR interaction effect on personality traits

Considering the possible epistatic effects between the SLC6A4 and *BDNF* genes (Kim, 2007, Pezawas, 2008, Terracciano, 2010b), exploration of interaction effect of the functional 5-HTTLPR × *BDNF* Val66Met polymorphisms on personality traits is of obvious interest. This issue was addressed in **Paper I**, where we used the data of both cohorts from the second study wave. At the time of assessment, participants in the younger cohort were 15 and older cohort 18 years old.

Indeed, our results showed a gene × gene interaction on personality traits. *BDNF* Met-allele carriers with the 5-HTTLPR S/S genotype scored lower on Conscientiousness than their peers (Figure 4). The effect of the Val66Met genotype on Conscientiousness mainly rested on its large effect in the S/S group. This effect was significant in Conscientiousness facets C1: Self-Efficacy and C4: Achievement Striving. Both of these facets are related to goal-orientation, accomplishment and achievement, and appear to be inferior in participants with this allelic combination. Additionally we found that *BDNF* Val-allele homozygotes with 5-HTTLPR S-allele carriers score lower in Openness to Experience facet O6: Liberalism. People with this allelic combination may thus prefer more traditional values.

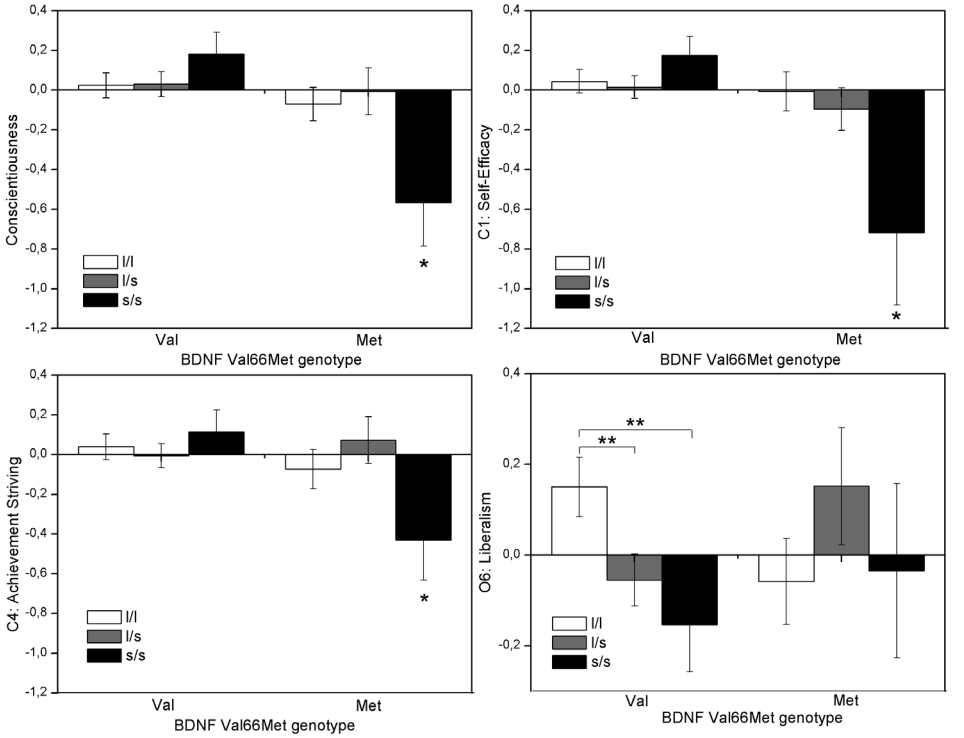

Figure 4. Significant interactions of 5-HTTLPR and *BDNF* Val66Met polymorphisms on personality traits and their facets. Pairwise comparisons made with Fisher's LSD test. * – $p < 0.05$ vs all other groups. ** – $p < 0.05$ between two groups.

Previous reports on 5-HTTLPR × *BDNF* Val66Met interactions have resulted with mixed findings. Pezawas and colleagues (2008) demonstrated an interaction effect on the volume reduction of anterior cingulate cortex, suggesting a protective effect of *BDNF* Met-allele in S-allele carriers. Others have identified 5-HTTLPR S/S genotype together with a *BDNF* Met-allele as a risk genotype for depression, but only in interaction with environmental factors (Kaufman, 2006, Kim, 2007). However, to our knowledge the only study reporting an 5-HTTLPR and *BDNF* interaction on personality traits in a large sample found the 5-HTTLPR L/L homozygotes to score lower on Neuroticism in the presence of two *BDNF* Val-alleles, whereas Met-allele carriers scored higher (Terracciano, 2010b). This effect technically differs from our results, where we demonstrated the lowest Conscientiousness scores in S/S homozygotes with at least one Met-allele present, but it should be born in mind that Neuroticism and Conscientiousness are in negative correlation in population-derived samples.

4.1.4.2. The interaction effect of *TPH2* G-703T and 5-HTTLPR polymorphisms on personality traits

The two principal proteins in the serotonergic neurotransmission, 5-HTT and TPH2 are both involved in the regulation of neurotransmitter levels available for release in the brain. Therefore the interaction of functional polymorphisms in genes encoding these proteins on behavioural measures, e.g. personality, can be expected. In **Paper III**, we aimed to study the possible G × G interaction effect on personality traits at age 15 and 18. We used data of both birth cohorts of ECPBHS with age-wise combined z-scores. An interaction effect on Conscientiousness at age 18 ($F(4, 816) = 2.99$, $p = 0.018$) was found. Indeed, the association of *TPH2* G-703T genotype with Conscientiousness was entirely dependent on the 5-HTTLPR genotype: the *TPH2* effect was evident only in 5-HTTLPR S-allele carriers (Figure 5).

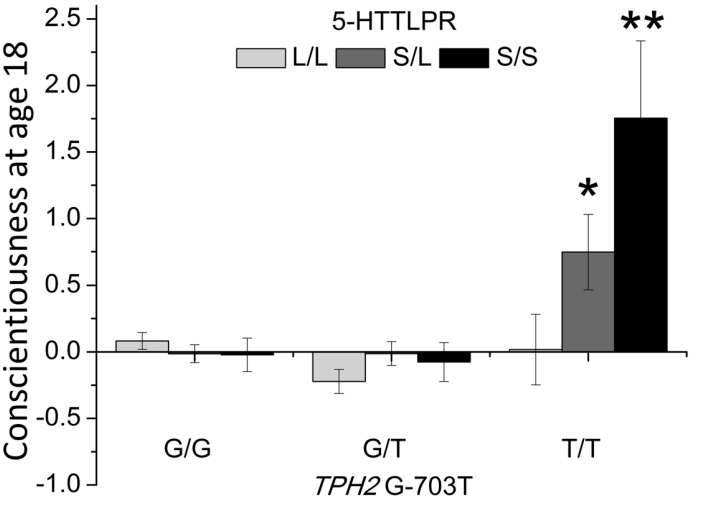

Figure 5. *TPH2* G-703T × 5-HTTLPR interaction effect on Conscientiousness at age 18. Data are expressed as z-scores +/– SEM. * – $p < 0.01$ *vs.* all *TPH2* G-allele carriers; ** – $p < 0.01$ *vs.* all *TPH2* G-allele carriers and all 5-HTTLPR L/L genotype groups (Fisher's LSD).

To the best of our knowledge there has been no previous report regarding *TPH2* × 5-HTTLPR interaction on FFM personality traits. This may well suggest that studies on smaller or less representative samples have missed the effect of the minority T-allele. Nevertheless, our findings are partially in accordance with the results of EEG and fMRI studies of emotional picture viewing and cognitive affective tasks, where carriers of the combination of *TPH2* T-allele and 5-HTTLPR short variant exhibited the greatest degree of neural activation in these tasks (Canli et al., 2008; Herrmann et al., 2007). Obviously, given the significantly smaller sample sizes in brain imaging studies, subjects with the

genotype combination of T/T-homozygotes and the S-allele would be rare, but measurement of the endophenotypes is closer to the gene than self-reported personality and hence expected to be more sensitive, even detecting the difference with a single T-allele of the *TPH2*. Additionally, Hahn and colleagues (2013) have reported a positive correlation between connectivity of amygdala and hippocampus, and Gray's trait anxiety (BIS) scores in individuals with the combination of *TPH2* G/G and 5-HTTLPR L_A/L_A genotypes. Interestingly, in the *TPH2* T-allele carriers with at least one 5-HTTLPR S or L_G-allele, a negative association was found instead (Hahn, 2013). Together with our findings on personality traits, it seems plausible that such an interaction between the two genotypes reflect a certain style of reaction to environment and putative changes in serotonergic neurotransmission may impact fundamental phenotypes, *i.e.* personality.

But in addition to G × G interactions on personality, also G × E interactions may play a pivotal role. Based on twin studies, the genetic component in personality is substantial, whereas shared environmental effects have little, if any, effect on personality traits (Bouchard and Loehelin, 2001). However, unique non-shared environmental effects seem to have more pronounced impact, but this in essence probably comprises several residual causes, e.g. measurement errors, chance and G × E interactions (Bouchard and Loehelin, 2001). Indeed, early environmental stressors, e.g. childhood adversities and trauma, may influence children's cognitive styles and moderate risk for a persistent state of negative emotionality, which, in turn, increase the probability of developing anxiety and mood disorders (Barlow, 2014). Furthermore, the combination of genetic predisposition and early life stress may sensitize key circuits within the brain, e.g. the hypothalamic–pituitary–adrenal (HPA) axis, in response to acute stress, leading to altered stress reactivity (Barlow, 2014). Therefore, the possible impact of genotype and stressful life events interaction effects on personality traits should be addressed in the future.

4.2. Associations of these functional gene variants with personality reflected in health-related and personality dependent behavior (Papers II, IV and unpublished data)

4.2.1. The impact of *BDNF* Val66Met genotype on food restriction in body weight regulation (Paper IV)

Eating disorders represent a group of mental illnesses characterized by abnormal eating behaviour, which harms individual's physical and mental health. Brain-derived neurotrophic factor has been regarded as a possible candidate molecule associated with the etiology of eating disorders. BDNF is widely distributed in the regions associated with regulation of eating behaviour

and energy intake, such as hypothalamic nuclei (Kernie et al., 2000). Evidence from the animal studies supports the role of *BDNF* in the modulation of 5-HT turnover and appetite (Lyons et al., 1999, Pelleymounter et al., 1995). In addition,hyperphagia and obesity are present in conditional mutant mice with complete deletion of BDNF (Rios et al., 2001). In humans, the *BDNF* Met-allele carriers are reported to have higher body mass index and increased obesity risk (Beckers et al., 2008). Furthermore, associations with disordered eating are supported by a meta-analysis, which concluded that Met-allele carriers have increased risk of developing an eating disorder compared with the Val/Val homozygotes (Gratacos et al., 2007), however, a more recent meta-analysis failed to detect associations between *BDNF* Val66Met and, specifically, anorexia nervosa (Brandys et al., 2013).

In **Paper IV**, we aimed to study the *BDNF* Val66Met effect on eating behaviour and body weight regulation in both birth cohorts of our study. The data were collected during the second study wave, when the participants of younger and older cohorts were 15 and 18 years old, respectively.

We found an interaction effect between the genotype and food restriction on scores of Bulimia among girls. More specifically, an interaction was found between Val66Met genotype and the reduction of meal frequency ($F(1,386) = 5.70$, $p = 0.02$) and between Val66Met genotype and starvation ($F(1,385) = 5.52$, $p = 0.02$). The Met-allele carriers who tried to regulate their body weight by reducing meal frequency or starvation scored higher on Bulimia subscale, i.e., they were more engaged in binge eating. In addition, a tendency to consume less calories in the food restrictive Met-allele carriers was observed, and this was statistically significant among the users of the most severe method, starvation (*BDNF* Val66Met × food restriction interaction on energy intake: $F(1,391) = 4.16$, $p = 0.04$). The interactions remained significant after the covarying effect of BMI was controlled for. There was no Val66Met genotype × food restriction interaction effect on Bulimia scores in boys, but bulimic behaviour in boys is infrequent.

Our results show the modulating effect of *BDNF* Val66Met polymorphism on the association between food restriction and binge eating, whereas Met-allele carriers are more vulnerable to the effect of food restriction to induce binge eating as compared to Val-homozygotes. Met-allele carriers have been reported to be more reactive to negative stimuli (Montag, 2008) and score higher on reward dependence (Itoh, 2004). The association of poor reward-related inhibition response with binge eating has also been shown in eating disorder patients (Rosval et al., 2006). It is thus possible that the *BDNF* Met-allele has a role in the development of eating disorders because it increases reward dependence, which enhances vulnerability to binge eating in subjects who engage in restrictive diets. Interestingly, these results correspond to our findings of the effects of *BDNF* Val66Met polymorphism on Conscientiousness on the same sample, assessed at the same time point (**Paper I**). The Met-allele carriers, who we also found more likely to practice binge eating while trying to restrict

food intake in **Paper IV**, scored significantly lower on Conscientiousness. As a trait for persistence, organization, self-discipline and orderliness, Conscientiousness has been found to be associated with disordered eating behaviour (Ghaderi and Scott, 2000, Podar et al., 1999). In a recent twin study a negative correlation between Conscientiousness and binge eating episodes was confirmed (Koren et al., 2014). In addition, the authors reported 45% of the covariance between Conscientiousness and binge eating to be due to additive genetic and 55% individual-specific environmental factors, which may therefore suggest shared etiological underpinnings with lack of control during binge eating episodes (Koren, 2014).

4.2.2. The effect of *COMT* Val158Met polymorphism on educational attainment, socioeconomic status and history of mood disorders (Paper II and unpublished data)

Personality is considered to be fully developed by the time of young adulthood (Costa et al., 1994). Our results indicate that, indeed, the *COMT* Val158Met genotype effects were more evident at age 25, compared to ages 15 and 18. Such genotype-dependent development of personality could be expected to have an influence on obtaining education, and educational achievements importantly shape the environment of the individual (Alvarez-Galvez et al., 2013, Lynch et al., 1997). The well-established effects of *COMT* genotype on the function of prefrontal cortex provide further reason to examine its possible impact on academic achievements, as both personality and cognitive abilities are of great importance in educational attainment. Therefore, in **Paper II**, we tested if *COMT* Val158Met genotype has an effect on participants' educational attainment by the age 25.

We found a genotype × gender effect on obtaining education. Males with Val/Met genotype had mainly obtained secondary or vocational education, whereas female heterozygotes had rather striven for higher education (Figure 6). Previously, several authors have reported no effect of *COMT* genotype on years of education or educational attainment (Liu et al., 2008, Martin et al., 2011, Sheldrick et al., 2008). One of the reasons for these negative findings could however be the structure and recruitment of samples. None of these samples has been population-representative, which could result in a bias due to the limited variability in the characteristics of study participants. Interestingly, Enoch and colleagues (Enoch et al., 2009) reported an interaction between *COMT* genotype and years of education affecting the scores of the Information (verbal comprehension and long-term memory) and Block Design (working memory) subscales of the WAIS-R. Interestingly, in the less educated group (crossover point 11–12 years), Met-allele carriers scored lower than Val homozygotes, whereas in the higher educated group Met-allele carriers had markedly better scores. According to the authors' interpretation, the Met-allele carriers need a good educational environment in order to develop their full potential for

superior cognitive skills compared to Val homozygotes. In case of adversity, their emotional vulnerability may deteriorate the development of cognitive skills. Thus, our finding that participants with the Val/Met genotype tend to have higher Conscientiousness scores than other genotypes is in line with the effect of *COMT* Val158Met genotype on education levels, but the direction of causality, if any, remains an open matter. People with high Conscientiousness scores are more organized, dutiful and self-disciplined. Therefore, they are more likely to be successful in all of their endeavors. However, although participants with the Val/Val genotype scored lower on Conscientiousness, in educational attainment by age 25, the heterozygotes differ from both of the homozygote groups. This effect could be explained with the Met homozygotes' vulnerability to stress and Val homozygotes' poorer cognitive performance, which both can affect the educational attainment. Also different adaptive strategies can play a role, heterozygotes possibly developing better coping strategies by the time of young adulthood than homozygotes. In addition, these strategies appear to differ between genders, which can explain the gender differences in the Val/Met group. For example, males with the Val/Met genotype may not have felt the pressure to obtain higher education, if there were faster options to success in the society.

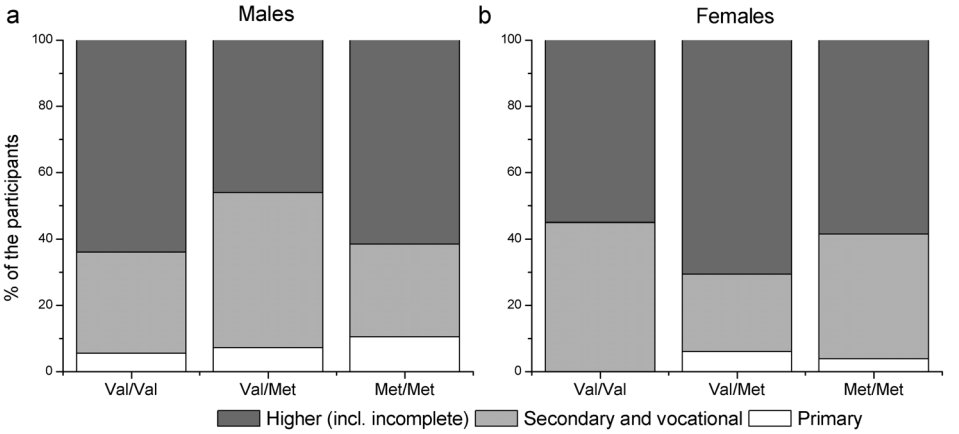

Figure 6. Educational levels by genotype and gender. Significantly higher than expected female *COMT* Val158Met Val/Met representation in higher education group, and lower representation of males (Chi-square = 13.6; df = 2; p = 0.001).

Low socioeconomic status is a strong predictor for a wide range of physical and mental health problems (Adler et al., 1994, Andrade et al., 2000, Lynch, 1997), and therefore we aimed to study the *COMT* Val158Met polymorphisms' effect on the monthly income and perceived socioeconomic status of the individual and the household. The *COMT* genotypes did not differ in terms of monthly income and monthly income of the household in either gender. Interestingly, heterozygote women assessed their socioeconomic status to be higher as

compared to both homozygote groups ($F(2,277) = 3.53$; $p = 0.03$). This may be related to their level of educational attainment. In addition, they tend to score lower on Neuroticism and higher on all other FFM personality traits than all remaining genotype groups. As the professional carriers unfold, further follow-ups may be more informative on whether or not the genotype-related differences in education will have an impact on other measures such as income.

In females, there was a tendency for Val-homozygotes to perceive their economic status of their household to be poorer as compared to both Val/Met heterozygotes and Met-homozygotes, although there were no differences in reported monthly incomes of the participants or their households. There were no differences between genotypes in the perceived socioeconomic status and economic status of the household in males. Recently it was confirmed that the Val-allele of *COMT* genotype increased in an allele-dose fashion the amygdala activity in response to fearful and angry facial stimuli. The effect was demonstrated only in females (Domschke, 2012). All this is in line with the notion that people with high Neuroticism experience more often negative affect which in turn manifests in negative bias in information processing.

Dysfunction in the major DA pathway in the brain, the mesolimbic/ mesocortical system, is proposed to contribute to the pathophysiology of depression (Nestler and Carlezon Jr, 2006). The *COMT* Val158Met variation is indeed found to modulate corticolimbic responses to emotional stimuli (Drabant, 2006, Smolka, 2005) and be involved in increased susceptibility to depression, stress and anxiety (Drury, 2010, Eley, 2003, Enoch, 2003, Hettema, 2008, Massat, 2004, Stein, 2005). Hence, we examined the effect of *COMT* polymorphism on the history of anxiety and mood disorders, and on the self-rated depressiveness (MÅDRS) and anxiety scores (STAI-S and STAI-T).

We did not observe any differences in genotype frequencies in individuals with anxiety and mood disorders and healthy controls in either gender. However, we detected a significant effect of *COMT* genotype on depressiveness at age 25 ($F(2, 485) = 4.97$, $p = 0.007$), whereas Val-homozygotes scored higher than other genotype groups (**Unpublished data**) (Figure 7). Regarding self-rated state and trait anxiety scores, we did not detect any significant genotype effects on STAI scores, but a tendency emerged on STAI-T ($F(2, 474) = 2.98$, $p = 0.052$), again showing the highest scores of the Val-homozygotes. To be noted, we did not find any gender differences in genotype effects on depressiveness nor anxiety scores.

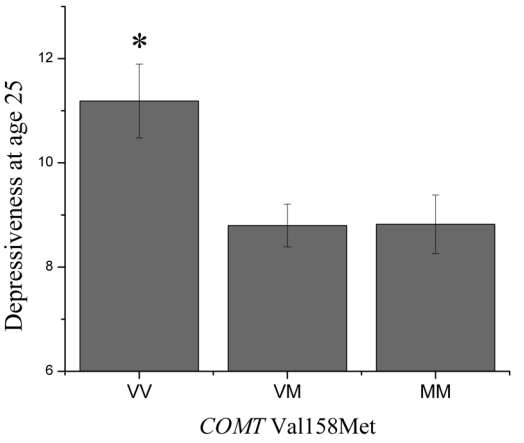

Figure 7. The effect of *COMT* Val158Met on depressiveness scores at age 25 (+/– SEM). * – $p < 0.001$ vs. all other groups; Fisher's LSD.

With these results we provide further evidence of Val/Val genotypes' effect on depressiveness. Nevertheless, previous studies have resulted in variable findings on depression, anxiety and negative emotionality, as some authors report the Met-allele and others the Val-allele to increase the susceptibility risk. One of the confounders may regard ethnicity of the subjects, as differences in genotypic distributions have been found across ethnic groups (Palmatier et al., 1999). In Caucasians, the Met-allele has often been associated with Neuroticism, but rather appears as decreasing the risk for anxiety and mood disorders. The Val-allele has been associated with higher phobic anxiety scale scores (McGrath, 2004), early onset of major depressive disorder in Caucasian samples (Massat, 2004), and the Met-allele has been found to be protective for depressive symptoms in children exposed to early social deprivation (Drury, 2010). Val/Val genotype has also been found to be more prevalent in suicide attempters than in normal controls, whereas in females it had an effect on the scores on STAXI (State-Trait Anger Expression Inventory) subscales Trait Anger and Anger Control (Baud, 2007). Parenthetically, our results also revealed the women with Val/Val genotype to score the highest on Anger subscale of the EE.PIP-NEO Neuroticism scale ($F(2, 450) = 6.12$, $p = 0.002$). In addition, a meta-analysis concluded that the Val-allele is associated with panic disorder in Caucasian and Met-allele in Asian samples, and these results were restricted only to females (Domschke et al., 2007). Regarding Asians, the Met-allele has also been associated to higher negative emotionality in females (Chen, 2011). Hettema and colleagues' study (Hettema, 2008) based on selected cases and controls from a large twin cohort found a haplotype of *COMT* Val158Met Val-allele with the A allele of rs165599 polymorphism to predict both higher Neuroticism and risk for anxiety disorders and major depression in a Caucasian sample, whereas these effects were again specific to females. Taken together, this issue needs further clarification on large ethnically homogeneous samples and the role of population differences as potential confounders should be taken into account in future meta-analytic studies.

4.2.3. Influence of *TPH2* G-703T polymorphism on mood and anxiety disorder symptoms (Unpublished data)

Considering the rate-limiting effects of TPH2 on serotonergic neurotransmission, the possible effect of *TPH2* gene variants on mood and anxiety disorders has been considered. As discussed in the introduction section, the *TPH2* G-703T polymorphism has been found associated with depression and higher amygdala reactivity to emotional stimuli, as well as with emotional instability. As described above, our results also indicate the *TPH2* G-703T effect on the personality traits Neuroticism and Conscientiousness. Thus we aimed to investigate the possible association of this gene variation with the scores of depressiveness inventories BDI and MÅDRS, as well as trait and state anxiety scores (STAI-S and STAI-T).

Data of depressiveness rating scales were available for both cohorts from the second and third study wave. STAI scores were collected from the younger cohort during second and third study wave, and only for the third study wave for the older cohort.

We did not find any genotype effect on the scores of depressiveness or anxiety rating scales. However, by the age 25, we detected a tendency for a G × G interaction effect with 5-HTTLPR genotype on STAI-T ($F(4, 468) = 1.99$, $p = 0.095$) and STAI-S ($F(4, 467) = 1.78$, $p = 0.132$). The *TPH2* T/T homozygotes with 5-HTTLPR S-allele compared to L/L homozygotes had a tendency of scoring lower on both STAI scales. This is in accordance with our findings regarding personality traits, where the subjects in the same genotype groups were scoring lower on Neuroticism and higher on Conscientiousness. Interestingly, by the age 25, we did not find these genotype associations with personality traits in older cohort, but instead a tendency towards lower anxiety. One of the possible explanations could be more pronounced social desirability in personality questionnaire responses by age 25, which may bias the variance of the personality scores. Another possible confounder may regard the environmental effects in developing psychiatric disorders. Indeed, the importance of life stress in depression etiology is well known (e.g. Fava and Kendler, 2000). More specifically, the genotype interactions with the number of stressful life events have been repeatedly reported to influence depression risk (Caspi, 2003, Kendler et al., 2005). Therefore the possible gene × environment effects should be addressed in the future.

Currently, regarding anxiety scales only data of the older cohort at age 25 are available. Hence, this possible G × G interaction on anxiety scores should be investigated again in the near future, when the presently ongoing data collection for younger cohort at age 25 has been completed and data of the two cohorts can be pooled for statistical analysis.

5. CONCLUSIVE REMARKS

The presence of a notable genetic component in personality development and depression etiology is generally well recognized. The rapid biotechnological advances are contributing to wider availability of genetic research methods in unraveling specific genetic loci underlying the vulnerability of depression and negative emotionality. However, regardless of some successes in detecting genetic risk variants, a lot still remains unknown.

With this dissertation, we have contributed in this field of research by demonstrating the effects of several depression- and anxiety-related common gene variants and gene × gene interactions on personality traits, potential risk factors in depression etiology. Furthermore, we show genotype effects on additional health-related factors, such as binge eating in body weight regulation, educational attainment, perceived socioeconomic status and depressiveness.

Although the *BDNF* Val66Met, *TPH2* G-703T and 5-HTTLPR polymorphisms have repeatedly been associated with Neuroticism and Harm Avoidance, interestingly we have found instead the main effects of *BDNF* Val66Met and *TPH2* G-703T on Conscientiousness, a trait for discipline, order and persistence, which is often linked to psychopathology and memory processes. In addition, we observed moderation by the 5-HTTLPR polymorphism, whereas subjects with a combination *BDNF* Val66Met Met-allele and 5-HTTLPR S/S genotype scored the lowest in Conscientiousness, but a combination of *TPH2* G-703T T/T and 5-HTTLPR S-allele yielded the highest scores. Genotype effects on Conscientiousness are not frequent findings; however this is not surprising considering the common usage of biased samples, e.g. university students. Therefore these preliminary results should be replicated in the future in unbiased samples.

We are not aware of any reports on the genotype interaction effects of *BDNF* or *TPH2* and 5-HTTLPR on Conscientiousness, but the results are not surprising, as such interactions have been found on several other depression-related phenotypes. As BDNF, TPH2 and 5-HTT are key elements in serotonergic neurotransmission, the interaction effects should have been expected.

Another important factor modulating the genotype effects is time, which allows the environmental effects and development to take place. Our results suggest the relevance of time and maturation in genotype effects on Neuroticism, as the effect of *COMT* Val158Met was most evident by the age 25; and the effect of *TPH2* G-703T was evident at age 15, but not 18. This implies the possible role of respective neurotransmitter systems in personality development and emphasizes the importance of future studies in longitudinal samples, being also compatible with the large difference in genes implicated in depression of childhood *vs.* adulthood (Harro and Kiive, 2011).

Genotypes under investigation also influenced other aspects of the lives of our subjects. The *BDNF* Val66Met Met-allele carriers, who we found to be with

low Conscientiousness, seem to be more engaged in binge eating while restricting food intake to regulate body weight. In addition, *COMT* Val158Met Val/Val homozygotes had the highest depressiveness scores and, furthermore, females with the Val/Met genotype, less neurotic than both homozygote groups, also had more likely pursued higher education by age 25 and assessed their socioeconomic status to be better. The subjects with the combination of *TPH2* G-703T T/T and 5-HTTLPR S-allele tended to score lower on anxiety scales by the age 25 as compared to the L/L homozygotes of 5-HTTLPR.

Considering the population representative nature of our sample and relatively young age of study participants, the findings of genotype effects on diagnostic criteria meeting anxiety and mood disorders would have been unlikely and indeed they were not found. Nevertheless, by studying the genotype effects on the results of anxiety and mood disorder inventories continuously, we could assess the possible risk of developing such disorders. Therefore, this issue should be addressed in the future to assess whether this possible risk will eventually lead towards a diagnosis of anxiety or mood disorder in the general population.

To conclude, the difficulties in unraveling the genetic foundations of personality traits and depression suggest a large number of additional factors, which may modulate the emergence of genotype effects. Our work on depression- and anxiety-related candidate genes in a large population representative sample highlights the significance of considering time, sex and gene × gene interactions as possible modulators of genotype effects. Moreover, it is important to invest into sample designs which enable to study genotype effects on complex behaviour in unbiased manner.

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SUMMARY IN ESTONIAN

Depressiooni ja ärevusega seotud geenivariandid: mõju isiksuseomadustele ja tervistmõjustavale käitumisele

Varasemate uuringute põhjal on teada, et mõned isiksuseomadused suurendavad depressiooni tekkimise riski. Üheks levinumaks selliseks isiksuseomaduseks peetakse Neurootilisust, mis näitab inimese kalduvust liigsele muretsemisele ja ärevuse tundmisele. Nii isiksuseomadustel kui ka depressioonil on aga tugev pärilik taust, seejuures osa geneetilisest alusest arvatakse neil olevat ühine. Kuid hoolimata jõudsatest arengutest biotehnoloogia valdkonnas ei ole siiani kummagi fenotüübi geneetilist alust suudetud tuvastada. Olulist rolli mängib siin kindlasti asjaolu, et tegemist on väga komplekssete tunnustega, millel on tõenäoliselt ka väga keeruline geneetiline taust.

Käesolevas väitekirjas uurisime suurel rahvastikupõhisel valimil, kuidas mõjutavad depressiooniga seotud geenivariandid isiksuseomadusi. Kõik uurimisalused geneetilised variandid on seotud aju neurotransmissiooniga - 5-HTTLPR ja *TPH2* G-703T polümorfismid serotoniini- ja *COMT* Val158Met dopamiinisüsteemiga, aga *BDNF* Val66Met neurotroofiliste funktsioonidega, mis on olulised närvirakkude arengu ja funktsionaalsuse tagamisel. Lisaks oli meie eesmärgiks teada saada, kas esineb ka nende geenide vahelisi interaktsioone, kas vanus mängib rolli ning lisaks, kas nimetatud geenivariandid võivad mõjutada ka muid tervise ja heaoluga seotud tegureid, nagu näiteks meeleolu- ja söömishäirete sümptomaatika, kõrghariduse omandamine ja sotsiaalmajanduslik staatus.

Leidsime, et kõik nimetatud kandidaatgeenid tõepoolest mõjutavad isiksuseomadusi rahvastikus. Täpsemalt, *BDNF* Val66Met Met-alleeli kandjad on madalama, kuid *TPH2* G-703T T/T genotüübiga isikud kõrgema Meelekindlusega, võrreldes teiste genotüübi gruppidega. Samas esines mõlema geenivariandi puhul ka interaktsioon 5-HTTLPR polümorfismiga, kusjuures kummagi genotüübi mõju oli kõige tugevam just 5-HTTLPR S/S homosügootide hulgas. *TPH2* T/T homosügootidel oli 15-aastaselt ka teistest palju madalam Neurootilisus, kuid kolm aastat hiljem oli see erinevus kadunud ning genotüübi mõju Neurootilisusele ei olnud. Lisaks leidsime ka *COMT* Val158Met mõju Neurootilisusele – Val/Val genotüübiga naised olid oluliselt neurootilisemad kui teiste alleelikombinatsioonidega naised. Huvitaval kombel avaldus genotüübi mõju alles 25-aastaselt, mis viitab ajafaktori olulisusele genotüübi efekti avaldumisel.

Edasi uurisime, kas nimetatud geenide mõju isiksusele võiks peegelduda ka teistes inimese tervise ja heaoluga seotud tegurites. Esiteks leidsime, et *BDNF* Val66Met polümorfism avaldab mõju ka söömishäirete sümptomaatika tekkimisel. Nimelt nende tüdrukute seas, kes püüdsid oma kehakaalu reguleerida toidukoguste vähendamise või näljutamise teel, esines Met-alleeli kandjail Val-homosügootidest oluliselt rohkem kontrollimatuid söömishooge, mida peetakse

söömishäire buliimia peamiseks sümptomiks. Lisaks leidsime, et *COMT* genotüübi Val-homosügootidel on kõrgem depressiivsus ja *COMT* genotüüp näib ka mõjutavat inimeste haridusteed. Nimelt 25ndaks eluaastaks oli kõige suurem hulk kõrgharidust omandavate inimeste hulk Val/Met naiste seas ning vastupidiselt, kõige vähem, Val/Met meeste seas. Lisaks olid just Val/Met genotüübiga naised need, kes hindasid oma sotsiaalmajanduslikku staatust teistest paremaks. Ka ei tuvastanud me *TPH2* mõju meeleoluhäiretele, kuid sellegipoolest leidsime G × G interaktsiooni tendentsi ärevusele 25-ndaks eluaastaks – *TPH2* T/T ja 5-HTTLPR S-alleeli kombinatsiooniga isikutel on madalam ärevus kui 5-HTTLPR L/L homosügootidel.

Kokkuvõttes, leidsime neurotransmissiooni mõjutavate geenivariantide mõju isiksuseomadustele, Neurootilisusele ja Meelekindlusele, suurel populatsioonipõhisel valimil ning lisaks kinnitasime, et need seosed peegelduvad ka teistes tervise ja heaoluga seotud tegurites. Käitumisgeneetika valdkonna ummikseis isiksuseomaduste, aga ka teiste keeruliste fenotüüpide geneetiliste aluste tuvastamisel viitab erinevatele moduleerivatele mõjuteguritele geeniefektide avaldumisel. Käesoleva väitekirja tulemuste põhjal rõhutame soo, vanuse ja geenidevahelise interaktsiooni arvestamise olulisust genotüüpide mõju uurimisel komplekssetele fenotüüpidele. Lisaks pole vähemtähtis, et paljud genotüübi efektid isiksuseomadustele saavad ilmneda vaid suurte ja kallutamata valimite uurimisel.

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Publications:

1. Passariello, C., Gruodyte, R., **Hiio, K**., Mäestu, J., Jürimäe, J., Saar, M., Cicchella, A., Stefanelli, C., Jürimäe, T. (2010). ADIPOQ SNP45 associated with lean body mass in physically active normal weight adolescent girls. *American Journal of Human Biology*, 22(6), 813–818.
2. Akkermann, K., **Hiio, K**., Villa, I., Harro, J. (2011). Food restriction leads to binge eating dependent upon the effect of the brain-derived neurotrophic factor Val66Met polymorphism. *Psychiatry Research*, 185(1–2), 39–43.
3. **Hiio, K**., Merenäkk, L., Nordquist, N., Parik, J., Oreland, L., Veidebaum, T., Harro, J. (2011). Effects of serotonin transporter promoter and BDNF Val66Met genotype on personality traits in a population representative sample of adolescents. *Psychiatric Genetics*, 21(5), 261–264.
4. **Lehto, K.**, Akkermann, K., Parik, J., Veidebaum, T., Harro, J. (2013). Effect of COMT Val158Met polymorphism on personality traits and educational attainment in a longitudinal population representative study. *European Psychiatry*, 28(8), 492–498.
5. Kurrikoff, T., **Lehto, K.**, Täht, K., Harro, J., Veidebaum, T. (2013). The 5-HTTLPR genotype and depressiveness link: Contribution of aspects of environment and gender. *Psychiatry Research*, 209(1), 126–127.
6. **Lehto, K**., Vaht, M., Mäestu, J., Veidebaum, T., Harro, J. (2015. Effect of tryptophan hydroxylase-2 gene polymorphism G-703T on personality in a population representative sample, *Progress in Neuro-Psychopharmacology & Biological Psychiatry,* 57, 31–35. DOI: 10.1016/j.pnpbp.2014.10.005

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Teaduspublikatsioonide loetelu:

1. Passariello, C., Gruodyte, R., **Hiio, K**., Mäestu, J., Jürimäe, J., Saar, M., Cicchella, A., Stefanelli, C., Jürimäe, T. (2010). ADIPOQ SNP45 associated with lean body mass in physically active normal weight adolescent girls. *American Journal of Human Biology*, 22(6), 813–818.
2. Akkermann, K., **Hiio, K**., Villa, I., Harro, J. (2011). Food restriction leads to binge eating dependent upon the effect of the brain-derived neurotrophic factor Val66Met polymorphism. *Psychiatry Research*, 185(1–2), 39–43.
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