DISSERTATIONES PSYCHOLOGICAE UNIVERSITATIS TARTUENSIS
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Serotonin-related biomarkers and symptoms of eating disorders

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Contribution of the author

The author of the present dissertation contributed to the publications as follows:

– for **Papers I and V**, collecting some of the data, conducting all the data analysis, and writing the publications as the main author.
– for **Papers II and IV**, participating in the study design, collecting some of the data, conducting all the data analysis, and writing the publications as the main author.
– for **Paper III**, creating the study design, collecting most of the data, conducting all the data analysis, and writing the manuscript as the main author.

ABBREVIATIONS

AN	anorexia nervosa
ANOVA	analysis of variance
AN-R	anorexia nervosa restrictive type
APA	American Psychiatric Association
BDNF	brain-derived neurotrophic factor
BED	binge eating diorder
BIS-11	Barratt Impulsiveness Scale, 11th version
BMI	body mass index
BN	bulimia nervosa
BN-P	bulimia nervosa purging type
CNS	central nervous system
DSM-IV-R	Diagnostic and Statistical Manual of Mental Disorders, 4th edition
ECPBHS	Estonian Children Personality, Behaviour and Health Study
ED	eating disorders
EDAS	Eating Disorders Assessment Scale
EDI-2	Eating Disorders Inventory – 2
EDNOS	eating disorders not otherwise specified
fMRI	functional magnetic resonance imaging
HPA-axis	hypothalamic-pituitary-adrenal axis
MADRS-S	Montgomery-Åsberg Depression Rating Scale self-reported version
MAO	monoamine oxidase
OCD	obsessive-compulsive disorder
OCPD	obsessive-compulsive personality disorder
PCR	polymerase chain reaction
SD	standard deviation
SNP	single nucleotide polymorphism
STAI	State and Trait Anxiety Inventory
TRP	tryptophan
5-HIAA	5-hydroxyindoleacetic acid
5-HT	5-hydroxytryptamine, serotonin
5-HTT	serotonin transporter
5-HTTLPR	serotonin transporter linked polymorphic region
β-PEA	β-phenylethylamine

I. INTRODUCTION AND REVIEW OF LITERATURE

I.1. Eating disorders

I.1.1. Classification and diagnoses

Eating disorder is a persistent disturbance of eating behaviour or behaviour intended to control weight, which significantly impairs physical health or psychosocial functioning (Fairburn & Walsh, 2002). Eating disorders (ED) are characterized by intense fear of weight gain and preoccupation with body image and body weight, which leads to extreme dieting and food restriction, and other dysfunctional weight control behaviours. In the Diagnostic and Statistical Manual of Mental Disorders 4th edition (DSM-IV-R), three broad categories are delineated: anorexia nervosa, bulimia nervosa, and eating disorders not otherwise specified (APA, 2000).

Anorexia nervosa (AN) is characterized by disturbed body image and abnormally low body weight, body mass index (BMI) lower than 17.5. Even though underweight, these individuals display morbid fear of fatness and weight gain. Extreme weight control methods like prolonged fasting and excessive exercising of a compulsive nature are common symptoms. Self-induced vomiting, spitting out food without swallowing, misuse of laxatives and diuretics are practised by quite a few anorexia individuals (Treasure et al., 2010). Symptoms of depression and anxiety disorders, irritability, lability of mood, impaired concentration, and obsessional features are frequently accompanying states (Fairburn & Harris, 2003). The disturbed eating behaviour results in physical symptoms like weakness and fatigue; gastrointestinal symptoms like constipation, fullness after eating, delayed gastric emptying; amenorrhoea, reduced libido and infertility; poor sleep with early morning wakening; hypothermia; osteopenia and osteoporosis; bradycardia and cardiac arrhythmias; metabolic and endocrine abnormalities (Pomeroy, 2004). The minimisation of symptoms and unwillingness to discuss eating behaviour can be observed at the initial phase of the illness.

Bulimia nervosa (BN) is characterized by recurrent episodes of binge eating in combination with some form of inappropriate compensatory behaviour like self-induced vomiting, misuse of laxatives, diuretics and appetite suppressing drugs (APA, 2000). The amount consumed during binge episodes varies (Kissileff et al., 2008), but binge eating could be best described as the sense of loss of control over food intake, which is accompanied by mood disturbances (Herzog & Delinsky, 2001). The binge episodes are followed by strict dietary restriction and attempts to reduce body weight. There is a subgroup of BN patients (6–8%) that does not exhibit purging behaviour but instead uses excessive exercising to compensate weight gain (Tobin et al., 1997; Striegel-Moore et al., 2001). Since BN patients have a normal BMI, the physical symptoms of BN

are often underestimated but purging induced medical complications (eg, electrolyte imbalances) can be life-threatening (Pomeroy, 2004).

Individuals with AN or BN judge their self-worth largely in terms of their shape and weight and their ability to control them (Fairburn & Harrison, 2003), thus sustaining the preoccupation with body image and body weight, which is also preserved by constant body checking (repeated weighing, mirror gazing, measuring the size of body parts) or avoidance of it.

The category of eating disorders not otherwise specified (EDNOS) encompasses eating disorders that do not meet full criteria for AN or BN (subthreshold AN or BN), show mixed features of both disorders, or extremely atypical eating behaviour (e.g. chewing and spitting out food without swallowing). Only one subtype of EDNOS, binge eating disorder, features it`s own set of diagnostic criteria (APA, 2000). Binge eating disorder (BED) is characterized by recurrent episodes of binge eating during which an unusually large amount of food is consumed in a discrete period of time, accompanied by a sense of loss of control over eating. Binge episodes are associated with at least three of the following: eating more rapidly than normal, eating until feeling uncomfortably full, eating large amounts when not feeling hungry, eating alone because of embarrassment, and feeling disgusted, depressed, or guilty after overeating. As in BN, the frequency criterion for binges is twice a week, although this criterion is not well supported for BN (Sullivan et al., 1998) and validated for BED (Striegel-Moore et al., 2000). Individuals with BED do not regularly engage in compensatory behaviours but it has been found that there are BED individuals who use laxatives and appetite suppressing drugs (Mizes & Sloan, 1998; Mond et al., 2006).

1.1.2. Epidemiology

The lifetime prevalence of ED in adult women in large community based samples has been reported as 0.6%–0.9% for AN, 1.1%–1.6% for BN, and 1.0%–3.5% for BED, and 0.1%–0.3%, 0.1%–0.5%, and 0.3%–2.0% respectively in men (Preti et al., 2009; Stice et al., 2009; Hudson et al., 2007; Garfinkel et al., 1995; Garfinkel et al., 1996).

The majority of epidemiological studies assessing ED prevalence do not report population rates of EDNOS (Thomas et al., 2009). The lifetime prevalence of subthreshold AN has ranged from 2.4 to 3.7% and for subthreshold BN from 2.5 to 6% (Favaro et al., 2003; Lewinsohn et al., 2000). Data show that 75% of women with ED in a community based study received the EDNOS diagnosis (Machado et al., 2007). Despite the perceived “subclinical” status of EDNOS, the studies indicate that individuals who receive this diagnosis exhibit psychopathology commensurate to that of AN and BN (Fairburn et al., 2007; Thomas et al., 2009).

The diagnostic cross-over between ED is common. Up to one- third of BN patients have a history of AN (Keel et al., 2000), and approximately 50% of

women with AN developed bulimic symptoms in a 15.5-year follow-up study (Bulik et al., 1997). Although data on diagnostic cross-over in EDNOS individuals is limited, approximately 40% of EDNOS individuals develop AN or BN within 1 year of initial symptom presentation (Milos et al., 2005).

1.1.3. Subtypes

In clinical practice the heterogeneity in symptoms, psychiatric comorbidity and personality traits can be observed in ED patients. Efforts to subclassify ED patients have emerged since DSM-IV was published. The distinction between a restrictive and a binge- purge type of AN as well as the distinction between a purging and a nonpurging type of BN has been made (APA, 2000). The utility and the validity of these subtypes have been questioned since. An individual`s diagnostic subtype designation may change over time, the most common patterns of crossover are from restrictive type of AN to binge-purge type of AN and from the latter to BN (Peat et al., 2009). Other cross-over patterns can be seen as well which suggests a lack of predictive validity for AN subtypes. Also, there is no convincing evidence for the utility and validity of nonpurging BN diagnosis. The differences found in BN subtypes are mainly quantitative rather than qualitative (Hoeken et al., 2009). The categorical approach has been a useful tool for clinicians and researchers but the assumption that ED are truly categorical in nature as opposed to dimensional does not have the sufficient level of construct validity (Gordon et al., 2007).

The research in the last decade has indicated that ED subtyping could benefit if personality differences would be taken into account. The subtyping based on personality profiles has been shown to be more effective than symptom-based subtyping in predicting level of functioning and clinical course (Keel & Mitchell, 1997; Westen & Harnden-Fischer, 2001). The presence of impulsive traits increases the risk for a poor treatment outcome and worser long-term prognosis in BN patients (Keel & Mitchell, 1997). Few studies that have examined personality disorders have found that Cluster B personality disorders, especially the borderline personality disorder, is associated with poor treatment outcome for ED (Lilenfeld et al., 2006). Thus, emotionally dysregulated/ impulsive patients show the poorest functioning, high comorbidity and the poorest treatment response (Thompson-Brenner & Westen, 2005). On the contrary, obsessive-compulsive personality disorder (OCPD) traits have been shown to be poor prognostic features among AN patients (Strober et al., 1997; Steinhausen, 2002).

1.1.4. Influence of dieting and trait-linked effects

It has long been debated whether symptoms in ED individuals are the cause or the consequence of malnutrition (Kaye, 2008). Since most of the studies have been carried out in patients who are in acute state of illness, it is difficult to differentiate between factors that predispose to the eating disorder and the changes brought about the disorder itself. The studies conducted on community based samples and recovered patients have been helpful to clarify the effects brought by traits or dietary restraint.

Food restriction has been considered to be a precursor of eating disorders, especially binge eating and bulimia nervosa (Polivy & Herman, 1985; Patton et al., 1999; Raffi et al., 2000). The relationship between dieting and the onset of eating disorders seems to be particularly strong for binge-type patients, and to a much lesser extent for restricting type AN patients (Jacobi et al., 2004). One possible explanation is that dieting fosters eating pathology because individuals may binge eat to counteract the effects of caloric deprivation. Experiments have shown that acute caloric deprivation (up to 19 hours) results in increased caloric intake among healthy controls and eating disorders patients (Telch & Agras, 1996; Hetherington et al., 2000). Though studies conducted in community samples on longer term milder diets (up to 8 weeks) do not consistently support the association between dieting and further binge eating (Stice, 2002). Also, the experimental study conducted in bulimia-spectrum patients reported that dietary restraint was not systematically elevated before binging, suggesting that dietary restraint may not be a direct antecedent to binge episodes (Engelberg et al., 2005) or its effect may be moderated by other factors. For example, it has been reported that impulsivity (poor response inhibition and the inability to delay gratification) is related to increased food intake and overeating (Davis et al., 2007; Guerrieri et al., 2008).

The meta-analysis by Stice et al. (2002) showed that there was significant heterogeneity in the effect sizes for the relation of self-reported dieting to eating pathology. Effect sizes were larger for studies that examined adolescents versus preadolescents or adults. Studies examining adolescents have greater power to detect effects possibly because this is the developmental period during which eating disturbances typically emerge (Stice et al., 1998; Stice et al., 2009).

It is acknowledged that mental disorders occur within the context of a pre-morbid personality structure that will often have a profound effect on the presentation and course of the disorder (Widiger et al., 1999). Often ED patients are characterised by variations on a compulsive to impulsive continuum. From the clinical point of view anorexia nervosa patients are described as anxious, constrained, obsessive and perfectionistic as opposed to bulimia nervosa patients who exhibit impulsive behaviour and emotional instability. This view is also supported by research data from comorbid psychopathology, showing that patients with AN restrictive type have higher prevalence of comorbid obsessive-compulsive disorder and obsessive-compulsive personality disorder, while

substance abuse is more prevalent in binge-purge type ED patients (for review see Lilenfeld et al., 2006).

However, studies have indicated that the division by personality traits is not always dependent on ED diagnosis. Obsessive-compulsive traits have been also found in BN patients and impulsive traits in AN patients (Aragona & Vella, 1998; Claes et al., 2002; Kaye et al., 2004). Recently Jacobs et al. (2009) showed that differences in personality traits and temperament were not related to anorexia nervosa subtype or clinical status. Likewise most studies comparing perfectionism levels across diagnostic groups have found no differences between ED subtypes (for review see Bardone-Cone et al., 2007). Also, ED subtypes do not differ from each other in behavioural measures of impulsiveness (Claes et al., 2006).

The cluster analytical studies show that three subtypes in patients with ED can be identified: emotionally dysregulated/impulsive, constricted/compulsive and high functioning/minimal personality pathology group (Goldner et al., 1999; Westen & Harnden-Fischer, 2001). This subdivision of ED patients was recently supported by the study of Wonderlich et al. (2005) who using the measures assessing psychiatric comorbidity determined the same pattern of clusters. The highly impulsive ED individuals showed elevated self-destructive behaviours and substance abuse, while affective-perfectionistic cluster was distinguished by high level of obsessionality, compulsivity, and perfectionism (Wonderlich et al., 2005). The tendency for ED patients to cluster into impulsive, inhibited/compulsive and low psychopathology subgroups was recently replicated by Steiger et al. (2009).

Majority of the individuals with AN or BN who exhibit perfectionism and obsessive-compulsive traits have these traits before the onset of ED (Fairburn, et al., 1997; Anderluch et al., 2003; Kaye et al., 2004) and these traits tend to persist even after recovery from ED (Deep et al., 1995; Srinivasagam et al., 1995; Von Ranson et al., 1999; Sutandar-Pinnock et al., 2003). The studies on premorbid impulsivity are limited. Trait impulsivity has been shown to have a small effect in predicting ED (Stice et al., 2002). Behavioural indicators of impulsivity such as delinquent behaviour, aggression and substance abuse have been shown to be better indicators of risk for the onset of ED (Wonderlich et al., 2004).

Moreover, malnutrition has been shown to exaggerate the premorbid traits in ED individuals (Pollice et al., 1997). The occurrence of binging and purging or sustaining the restrictive eating has been shown to associate with impulsivity and compulsivity (Vervaet et al., 2004; Claes et al., 2005). In a recent experiment it was shown that individuals who restrict their food intake binge eat more likely when they have high levels of impulsivity (Jansen et al., 2009). Thus, impulsive-compulsive traits may moderate the relationship between dietary restraint and further eating behaviour.

1.2. Serotonin system and eating disorders

1.2.1. Serotonin activity and its effect on eating behaviour

Serotonin (5-HT) is involved in a broad range of biological, physiological and behavioural functions such as motor activity, eating, sleep and thermo-regulation, cardiovascular and respiratory activity, as well as the modulation of affective states (Lucki, 1998). Serotonergic neurons project from the raphé nuclei to virtually all parts of the central nervous system including hypothalamus which is involved in regulating food intake. 5-HT is synthesized from the aminoacid tryptophan (TRP), thus variations of TRP content in food are capable of increasing or decreasing 5-HT synthesis (Fernstrom & Wurtham, 1971). Food restriction significantly lowers plasma TRP, resulting in a decreased plasma ratio of TRP to neutral amino acids, and in turn, a reduction in the availability of TRP to the brain (Biggio et al., 1974; Anderson et al., 1990).

5-HT is metabolised by monoamine oxidase (MAO) that occurs in two isoenzymes, MAO-A and MAO-B. Although most tissues express both forms of MAO, human placentae and fibroblasts express predominantly MAO-A, and platelets and lymphocytes express only MAO-B (Shin et al.,1999). Because multiple biochemical and pharmacological similarities exist between blood platelets and 5-HT containing neurons of the CNS the platelet has been considered as a model for studying central serotonergic functioning (Da Prada et al., 1988) and platelet MAO activity has been proposed as a peripheral indicator for the cerebral 5-HT activity (Oreland & Shaskan, 1983). The platelet MAO activity is strongly correlated to cerebrospinal fluid levels of the 5-HT metabolite 5-hydroxyindoleactic acid (5-HIAA) (Oreland, 1981; Fahlke et al., 2002).

Using various pharmacological treatments, including the administration of tryptophan, 5-HT re-uptake inhibitors and releasing drugs or 5-HT receptor antagonists, it has been demonstrated that 5-HT manipulations give rise to specific changes in feeding parameters (Blundell, 1986). Manipulations that increase 5-HT activity lead to reduced eating (Goodwin et al., 1987), whereas manipulations that decrease 5-HT activity precipitate binge eating (Smith et al., 1999).

Abnormalities in 5-HT function have been found in ED patients. In comparison with healthy controls patients with anorexia nervosa (AN) have a significant reduction in basal concentrations of the 5-HT metabolite cerebrospinal fluid 5-HIAA during the acute phase of illness (Kaye et al., 1984), reduced platelet [3H] paroxetine binding (Bruce et al., 2006) and lower platelet MAO activity (Diaz-Marsa et al., 2000). Yet, levels of CSF 5-HIAA have been found to be significantly elevated following a period of long term recovery in AN. These results have led to the suggestions that AN may actually correspond to a primary state of increased 5-HT activity, which during the phase of active illness is masked by malnutrition-induced reductions in 5-HT activity (Kaye et al., 1991). Kaye et al. (2003) have demonstrated that dietary-induced reduction of

TRP was associated to decreased anxiety both in ill and recovered AN patients suggesting that food restriction helps to avoid the excessive anxiety and dysphoric mood.

Bulimia nervosa (BN) patients have reported to have lower platelet MAO activity (Hallman et al., 1990; Carrasco et al., 2000; Podar et al., 2007) as well as lower cerebrospinal fluid 5-HIAA concentrations than controls (Jimerson, 1992). Also, blunted neuroendocrine responses following challenge tests have been consistently found in BN patients (Brewerton et al., 1992; Levitan et al., 1997; Steiger et al., 2001). Fully active bulimic patients have been found to display reduced density of platelet paroxetine-binding sites, and the finding was similar to remitted bulimic patients (Steiger et al., 2005a). Recovery from BN is also reported to coincide with normal endocrine responses after 5-HT agonists (Wolfe et al., 2000) and abnormally high cerebrospinal fluid 5-HIAA concentrations (Kaye et al., 1998).

Although it has been shown that alterations in serotonergic activity contribute to various expressions of eating pathology it is not clear which changes in 5-HT function observed in eating disorders patients represent trait vs state effect.

1.2.2. Compulsive-impulsive traits, serotonergic activity and eating disorders

In general population as well as in psychiatric patients obsessive-compulsive traits and behavioural inhibition is associated to higher levels of 5-HT (Swedo et al., 1992; Fineberg et al., 1997; Bengel et al., 1999; Cath, 2001; Dickel et al., 2007) while impulsivity and affective instability has been associated with lower 5-HT levels (Lesch & Mössner, 1998; Paris et al., 2004; Gonda et al., 2006). The data show that experimentally induced alterations in 5-HT pathways produce changes in affect related behaviours. Studies looking at the effect of serotonin function on aggressive and hostile behaviour investigated by manipulation of TRP in non-clinical samples show that individuals high in aggressive tendencies become more aggressive, irritable and hostile after TRP depletion, and less so after TRP enhancement, with no effect among individuals low in aggressive tendencies (Cleare & Bond, 1995; Marsch et al., 2002). In another study conducted in a community based sample low 5-HT function was related to impulsivity (measured by BIS-11) and angry hostility, while high 5-HT response was related to higher conscientiousness (Manuck et al., 1998). The studies using the challenge tests indicate that mainly the motor and cognitive impulsivity is associated with a blunted serotonergic response, while impulsivity which is related to risk taking is related to dopaminergic system (Hennig, 2004).

There have been suggestions that 5-HT status in eating disorders needs to be understood as covarying with trait characteristics like impulsivity and compulsivity (Steiger et al., 2003). Reduced 5-HT activity has been associated to

self-injurious behaviour (Steiger et al., 2001) and co-morbid borderline personality disorder (Steiger et al., 2005b) in ED patients. This is in conjunction with findings from other psychiatric patients that link self-harming and impulsive behaviour to blunted serotonergic response (New et al., 1997; Soloff et al., 2000; Paris et al., 2004). Rigid and obsessive behaviour has been experimentally shown to be present in a subgroup of ED patients (Roberts et al., 2007). Family-genetic studies show that features of OCPD and ED share a common familial cause (Lilenfeld et al., 1998; Lilenfeld et al., 2000), suggesting that obsessive behaviour may be partially genetically determined risk factor for ED. Steiger et al. (2004) have reported that high 5-HT activity as measured by paroxetine–binding density was associated with increased compulsivity and perfectionism in women with bulimia-spectrum disorders.

Data from neuroimaging studies show that altered 5-HT function persists after recovery from ED symptoms (Bailer et al., 2004; Kaye et al., 2005; Bailer et al., 2007) lending further support to the notion that 5-HT-ergic activity in ED patients may reflect variations in compulsive-impulsive traits.

1.2.3. The serotonin transporter gene promoter polymorphism (5-HTTLPR)

5-HT activity in the brain is regulated by a sodium-chloride-dependent transporter (5-HTT) located in the plasma membrane of the cell (Blakely et al., 1991). The serotonin transporter (5-HTT) plays an important role in serotonergic neurotransmission by facilitating 5-HT reuptake from the synaptic cleft (Heils et al., 1996). The 5-HTT is regarded as the initial sites of action of antidepressant drugs and several potentially neurotoxic compounds (Lesch & Gutknecht, 2005).

The function of 5-HTT itself is under genetic control. The transcriptional activity of the 5-HTT gene is modulated by 5-HTT gene-linked polymorphic region (5-HTTLPR). *In vitro* studies of human lymphoblastoid cells show that the short or *s*-allele in the 5-HTTLPR is associated with lower transcriptional activity of the promoter as compared to the homozygosity for long or *l*-allele, and has been suggested to lead to lower expression of 5-HTT mRNA, less 5-HT binding, and less 5-HT reuptake (Lesch et al., 1996). Human neuroimaging studies of 5-HTT availability (Parsey et al., 2006; Shioe et al., 2003) and postmortem studies of 5-HTT bindings (Lim et al., 2006) have not detected consistent effect of the 5-HTTLPR. However, the allelic differences in the 5-HTTLPR have been demonstrated to affect brain volume and gray matter density in multiple brain regions in humans (Canli et al., 2005; Pezawas et al., 2005) and non-human primates (Jedema et al., 2010).

Recently the existence of a *l*-allele variant, Lg (*l*-allele with A → G substitution), closely equivalent in it`s expression to *s*-allele was reported (Hu et al., 2006). However, this finding has not been consistently replicated (Martin et al., 2007).

The *s*-allele of the 5-HTTLPR has been suggested to lead to the development of less efficient and less flexible 5-HT system, and has been associated to different forms of psychopathology, especially affective instability (Lesch & Mössner, 1998), impulse control deficiencies (Retz, 2004), impulsive suicide attempts (Anguelova et al., 2003; Baca-Garcia et al., 2005) and alcohol dependence (Lichtermann et al., 2000). Most neuroendocrine tests of central serotonergic function have shown blunted responses in *s*-allele carriers. Hariri et al. (2002) reported that individuals with at least one copy of the 5-HTTLPR *s*-allele exhibit greater amygdala responsivity, as assessed by fMRI, in response to fearful stimuli. Also *s*-allele carriers have been shown to have greater and longer lasting reactions to fearful stimuli (Armbruster et al., 2009). The imaging genetics studies show that the *s*-allele leads to reduced gray-matter volume in limbic regions and disrupted amygdala-cingulate coupling after emotional stimuli (Heinz et al., 2005; Pezavas et al., 2005). The latter result correlated with harm avoidance, suggesting that strong amygdala activity free from anterior cingulated control may be responsible for anxiety related traits associated with the 5-HTTLPR.

Contrary to the *s*-allele, homozygosity for *l*-allele of the 5-HTTLPR is associated with higher 5-HTT expression and thus with greater 5-HT transport capacity (Lesch et al, 1996; Greenberg et al., 1999). Several studies have shown the enhanced 5-HTT function in the pathophysiology of obsessive-compulsive disorder (OCD) and autism, based on an overrepresentation of the high-activity *l*-allele (McDougle et al., 1998; Bengel et al.,1999; Hu et al., 2006; Dickel et al., 2007).

1.2.4. The 5-HTTLPR and eating disorders

Although several lines of evidence indicate that disturbances of 5-HT neurotransmission contribute to various expressions of eating pathology, studies conducted on 5-HTTLPR in eating disorder patients have not given clearcut associations between the 5-HTTLPR genotype and eating disorders. While some studies have reported the association between the 5-HTTLPR *s*-allele and eating disorders (Di Bella et al., 2000; Fumeron et al., 2001), most studies have found no allelic differences in the 5-HTTLPR in eating disorder patients (Hinney et al., 1997; Sundaramurthy et al., 2000; Lauzurica et al., 2003; Monteleone et al., 2006; Steiger et al., 2005b; Racine et al., 2009). Among BN patients the *s*-allele carriers display higher psychiatric comorbidity like major depressive disorder, anxiety disorders and substance abuse (Richardson et al., 2008), higher harm avoidance (Monteleone et al., 2006), as well as affective instability, insecure attachment, and impulsivity (Steiger et al, 2005b). A neuroimaging study reported the *s/s* homozygous individuals to have reduced 5-HTT binding even after recovery from ED (Bailer et al., 2007). The effect of the *s*-allele of the 5-HTTLPR on affect has been described in population-derived samples (Gonda et al., 2005; Gonda et al., 2006) and may thus reflect a general

dimensional modulatory role of the serotonergic system that contributes to severity but not presence of symptoms.

Recently Steiger et al. (2009) reported that the frequency of the 5-HTTLPR *La/La* genotype was highest in the subgroup of ED patients who were markedly inhibited and compulsive, arguing that this genotype may increase the expression of obsessive compulsive traits in ED individuals. A study on a non-clinical Japanese population found the *l/l* genotype to be more frequent among subjects with abnormal eating attitudes (Matsushita et al., 2002). Since there are differences in genotype frequencies between Caucasian and Asian populations, the latter possessing *l/l* genotype less frequently (Nakamura et al., 1997), these results are not directly comparable to the studies conducted in Caucasian populations.

1.2.5. The influence of the 5-HTTLPR × adverse life events on psychopathology

Growing body of evidence suggests that emotional reactivity and stress response can be influenced by early life experiences, and that severe life trauma may increase the risk for anxiety and affective disorders (Lesch & Gutknecht, 2005). Although the association between stressful life events and psychopathology in general has been studied extensively, only some researchers have investigated the relationship between adverse life events and the onset of an eating disorder. There is some evidence that the onset of AN and BN is associated to adverse life events (Horesh et al., 1995; Welch et al., 1997). These adverse life events may be associated to body weight and shape-related harmful experiences like teasing and bullying (Wade et al., 2007; Sweetingham & Waller, 2008) or severe traumas like sexual and physical abuse (Johnson et al., 2002). Also, the association between stressful life events with extreme weight control behaviours and binge eating has been reported in a community based sample of adolescents (Loth et al., 2008) and young adults (Smyth et al., 2008).

Gene-environment interactions occur when an environmental stressor is more likely to lead to negative outcomes in the presence of a risk genotype, or the effect of exposure to an environmental pathogen activates genetic susceptibility (Moffitt et al., 2005). Caspi et al. (2003) reported that individuals with one or two copies of the 5-HTTLPR *s*-allele exhibited more depressive symptoms and suicidality in relation to stressful life events than did individuals homozygous for the *l*-allele. Since then the replication studies looking at the gene× environment effect in the development of affective disorders have been growing rapidly (Kendler et al., 2005; Wilhelm et al., 2006; Cervilla et al., 2007). Moreover, the development of a less efficient serotonergic system has been demonstrated among the 5-HTTLPR *s*-allele carriers who had adverse life events in the early age (Lesch & Gutknecht 2005). However, the research conducted in ED patients in this field is rather limited. Yet, one possible explanation of the inconsistent results of the association between the 5-HTTLPR and eating disorder symptoms may be because the history of adverse life events has

not been taken into consideration. One of the few studies conducted in ED field about serotonergic activity and stressful life events found that BN patients with reduced platelet paroxetine binding (as compared to those with higher binding) had experienced more childhood sexual abuse (Steiger et al., 2004).

The data from patients with affective disorders suggests that the *s*-allele carriers are more sensitive and reactive to life circumstances. Since eating disorders are often comorbid with affective disorders (Mangweth et al., 2003) and there is a subgroup of ED patients who display impulsive behaviour and difficulties in affect regulation, their eating disturbances may be related to sensitivity to environmental stressors moderated by the 5-HTTLPR.

1.2.6. Brain-derived neurotrophic factor and its role in eating behaviour

Neurotrophins are a family of structurally related growth factors (nerve growth factor, the brain-derived neurotrophic factor, and the neurotrophins 3 and 4/5) that enhance the survival and development of neurons in the central and peripheral nervous systems (Davies, 1994). Brain-derived neurotrophic factor (BDNF) plays an important role in regulating synaptic activity and plasticity of mature neurons (Poo, 2001). It is widely distributed in the CNS, including regions associated with regulation of eating behaviour and energy intake, such as hypothalamic nuclei. (Kernie et al., 2000; Yan et al., 1997). Interaction between BDNF and 5-HT function has been demonstrated in animal models. The infusion of BDNF increases 5-HT turnover in the hypothalamus and dose-dependently suppresses appetite in adult rats (Pelleymounter et al., 1995), whereas 5-HT turnover is reduced in heterozygous BDNF knock-out mice who display hyperphagia and accompanied weight gain (Lyons et al., 1999).

The most studied polymorphism of the BDNF gene (SNP rs6265, Val66Met), converts a valine to methionine in the 5`pro-region of the human BDNF gene altering the intracellular trafficking and packaging of pro-BDNF and thus the secretion of BDNF (Egan et al., 2003), leading to less efficient intracellular pro-BDNF trafficking and impaired activity-dependent BDNF secretion (Chen et al., 2004). The met-allele of the BDNF Val66Met polymorphism has been associated with eating disorders (Ribases et al., 2003; Ribases et al., 2004; Mercader et al., 2007). A meta-analysis showed that the met-allele carriers have a 36% higher risk of developing an eating disorder than people with the val/val genotype (Gratacos et al., 2007), the underlying mechanism of its contribution is not known though. Recently Xu et al. (2003) reported that in mice food deprivation reduced the level of BDNF mRNA by 60% in the ventromedial hypothalamic nuclei suggesting that nutritional state plays an important role in the expression of BDNF. Thus, given the strong rationale from animal studies, the met-allele carriers, having a reduced secretion of BDNF could be especially vulnerable to the effects of food restriction on later food consumption, as extreme dietary restrictions have been shown to lead to binge eating (Polivy & Herman, 1985; Raffi et al., 2000).

2. AIMS OF THE STUDY

Available evidence suggests that eating disorders are associated with disturbances in serotonergic functioning. Moreover, serotonin-related biomarkers have been shown to correlate with personality-related variability within the eating disorder subtypes. The aim of the present thesis was to explore whether the markers of the serotonin system may help to explain the heterogeneity in eating disorder symptoms and related traits.

More specifically the aims of the dissertation were:

- to examine whether two markers of the serotonergic system, platelet MAO activity and the 5-HTTLPR, are associated with symptoms of eating disorders;
- to explore whether the associations between the 5-HTT gene polymorphism and eating disorder symptoms are related to impulsive traits;
- to analyse the relationship between allelic differences in the 5-HTTLPR and compulsive traits in eating disorder patients;
- to explore the role of interaction of the 5-HTTLPR and adverse life events on eating disorder symptoms;
- to examine whether the BDNF Val66Met genotype influences the symptoms of eating disorders, and the accompanying role of food restriction on these symptoms.

3. MATERIALS AND METHODS

3.1. Participants

3.1.1. Population-based sample (Papers I, II, IV, and V)

The main sample used in the current thesis is based on both cohorts of the European Youth Heart Study (EYHS) conducted in Estonia in 1998/99, which was incorporated into the longitudinal Estonian Children Personality, Behaviour and Health Study (ECPBHS) (Harro et al., 2001). All schools of Tartu City and County, Estonia, which agreed to participate in the study, were included into the sampling using the probability proportional to the number of children of the respective age group in the school. Totally, 1176 children from 25 schools were participating in the first wave of the study. The data presented in the thesis were collected during the second and third follow-ups. During the second follow-ups in 2001/2002 and 2004 82% of the original sample was recruited. Altogether 426 girls (mean age 16.1 ± 1.6) and 341 boys (mean age 16.1 ± 1.5) were included to the analysis (**Paper I, V**). During the third follow-up in 2007–2009 we were able to recruite 78% from the original sample. The participants were also screened for eating disorders by self-report questionnaire during this study wave. The data was obtained from 560 women (mean age 21.6 ± 3.5) and 431 men (mean age 21.5 ± 3.6) (**Paper II**). The results presented in **Paper III** are based on the data from adolescent girls of the younger cohort who participated both in the second and the third follow-up. The data of 261 girls (mean age 14.8±0.5) and 252 girls (mean age 17.8±0.5) from the second and third wave respectively was analysed.

The data were collected in the laboratory in all study waves. Height and weight were measured in light clothing by standardised procedures to calculate BMI.

Adolescents and their parents gave their written informed consent in all study waves. The study was approved by the Ethics Review Committee on Human Research of the University of Tartu.

3.1.2. Eating disorders patients and healthy controls (Paper III)

ED patients were recruited from the inpatient unit of Tartu University Clinics Eating Disorders Centre. The control group was recruited through school/university announcements, from employers of public service and different private service branches. Data was collected during the years 2007 – 2008. The sample comprised altogether 143 women, of those 90 were eating disorders patients and 53 age and education matched healthy controls.

In patients the diagnostic assessment was carried out by a psychiatrist and in the control group by a clinical psychologist according to DSM-IV-TR diag-

nostic criteria (APA, 2000). The blood samples and data about eating behaviour and attitudes from the ED group were collected during the first days of hospitalization, and other psychological measures were completed following days. Height and weight were measured by standardized procedures on the date of the interview. In case of acute physical state patients were recruited to the study 2–3 weeks after the beginning of treatment.

Based on diagnostic criteria the patient group involved individuals with BN purging type (BN-P), n = 37; binge eating disorder (BED), n = 15; anorexia nervosa restricting type (AN-R), n = 31; anorexia nervosa purging type (AN-P), n = 3 and subthreshold AN (all of the criteria for AN were met except that the individual had regular menses, or the low weight criterion for AN not met), n = 4. Since the similarity of eating pathology the patients were merged into the binge (BN-P, BED patients) and the restrictive group (subthreshold AN, AN-R, AN-P patients). The descriptive characteristics of the sample are given in **Table 1, Paper III.**

The study was approved by the Ethics Review Committee on Human Research of the University of Tartu, and written informed consent was obtained from all the participants.

3.2. Measures

3.2.1. Eating Disorders Inventory-2 (Papers I, II, IV,V)

Eating Disorders Inventory-2 (EDI-2; Garner, 1991) Estonian version (Podar et al., 1999) two subscales – Drive for thinness and Bulimia – were used to assess eating behaviour and attitudes. 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). The suggested cut-off point for Bulimia subscale (>6) (Norring and Sohlberg, 1988) was used to determine a high-risk group for binge eating.

3.2.2. The self-report questionnaire based on DSM-IV diagnostic criteria (Papers II)

The self-report questionnaire based on DSM-IV-R diagnostic criteria for eating disorders (APA, 2000) was used to detect subjects with eating disorders. The participants were asked the questions in yes/no format, followed by the questions about the frequency of the symptoms if necessary (for example: *During the past 6 months have there been times when you have had binge eating episodes when you ate an unusually large amount of food? During the episodes when you ate an unusually large amount of food, did you experience a loss of*

control? How many days per week/per month over the past 6 months have you had the binge eating episodes?).

3.2.3. Eating Disorders Assessment Scale (Paper III)

Eating Disorders Assessment Scale (EDAS) is a 29-item self-report scale derived from the original 86-item scale. Items were answered on a 6-point scale (from "never" to "always"). As a result of the factor analysis (principal component method) 4 factors were extracted which explained 65.8% of the total variance. The subscales were named Restrained eating, Binge eating, Purging and Preoccupation with body image and body weight (Akkermann et al., unpublished manuscript). While the first three subscales measure the behavioural component of disturbed eating behaviour, the latter subscale measures the cognitive-affective component (*I am bothered by thoughts that people may criticize the way I look*; *I think if I was thinner I would be more successful*). The scale was designed to screen people with ED from the population sample and also discriminate patients with AN, BN, and BED. EDAS subscales show good internal consistency (Cronbach $\alpha = 0.90–0.93$) and discriminant validity. Binge Eating and Purging subscales and the total score of EDAS discriminated AN, BN, and BED patients from each other. Restrained eating and Preoccupation with body image and body weight subscales appeared to assess latent dimensions common to eating disorders. Construct validity of the scale was confirmed by strong correlations with the EDI-2 subscales that measure eating disorders symptoms (i.e. Bulimia, Body Dissatisfaction and Drive for Thinness).

3.2.4. The Mini-International Neuropsychiatric Interview (Paper III)

The Mini-International Neuropsychiatric Interview (Sheehan et al, 1994) M.I.N.I.5.0.0. is a short structured psychiatric interview developed to diagnose DSM-IV and ICD-10 mental disorders. M.I.N.I. 5.0.0 was adapted into Estonian by the Department of Psychiatry, University of Tartu.

3.2.5. Structured Clinical Interview for DSM-IV-TR Axis I Disorders (Paper III)

Expanded version of the eating disorders module of the Structured Clinical Interview for DSM-IV-TR Axis I Disorders (SCID-I/NP; First et al., 2002) was used if necessary to specify eating disorder diagnoses.

3.2.6. 48-hour food record (Paper V)

Participants were asked to keep a food record during two days prior to coming to the study, followed by a face-to-face interview in the next day. The data from the interview was compared to the food record and the discrepancies were discussed with the participant. Portion size which was not indicated in the food record was estimated using pictures of portion sizes. Nutrient intake was analysed by Micro Nutrica 2.0. (Knuts et al., 1993). Based on food record the avarage daily calorie consumption was calculated.

3.2.7. Body weight regulation (Paper V)

Participants were asked in the format of self-report questionnaire 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 have 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.

3.2.8. Barratt Impulsiveness Scale (Paper II)

Barratt Impulsiveness Scale 11th version (BIS-11) (Patton et al., 1995) was designed to assess different aspects of impulsiveness: motor impulsiveness, attentional impulsiveness and non-planning impulsiveness. In Estonian version 27 out of the original 31 items formed a single scale with average inter-item correlation r = 0.13, and Cronbach alpha coefficient 0.80 (Paaver et al., 2007). It has been demonstrated that subscales of BIS-11 are moderately inter-correlated (Stanford et al., 2009), and in a common factor analysis with other measures of impulsivity all three subscales had significant loadings into the same factor (Miller et al., 2004; Whiteside and Lynam, 2001). In data analyses the total score of BIS-11 was used.

3.2.9. State and Trait Anxiety Inventory (Paper II, IV)

State and Trait Anxiety Inventory (STAI; Spielberger et al., 1983) is a 40-item scale measuring state and trait anxiety. While state anxiety is fluctuating, the trait anxiety refers to the stable individual differences in anxiety proneness.

3.2.10. Estonian Multidimensional Perfectionism Scale (Paper III)

Estonian Multidimensional Perfectionism Scale (Pullmann et al., unpublished manuscript) has been constructed on the bases of Frost Multidimensional Perfectionism Scale (Frost et al., 1990) and Hewitt and Flett`s (1991) Multidimensional Perfectionism Scale. As a result of the factor analysis 4 factors were extracted named similarly to the original subscales: Personal Standards, Organization, Parental Expectations/Criticism and Concern over Mistakes. Items (7 for each factor) were answered on a 5-point scale ranging from 0 (*strongly disagree*) to 4 (*strongly agree*). The internal reliability coefficients (Cronbach alphas) of the subscales were 0.94, 0.83, 0.86, and 0.92, respectively.

3.2.11. Montgomery-Åsberg Depression Rating Scale self-reported version (Paper IV)

The self-reported version of Montgomery-Åsberg Depression Rating Scale (MADRS-S; Svanborg & Åsberg, 1994) is a 9 item scale constructed on the bases of the original expert-rated scale of MADRS (Montgomery & Åsberg, 1979). The MADRS-S has been shown to have a high concordance with MADRS (Mattila-Evenden et al., 1996).

3.2.12. Adverse life events (Paper IV)

The list of adverse life events was constructed for the ECPBHS study and consisted of 30 adverse experiences including parental death and divorce/ separation, living in institution or under foster care, unemployed parent, parental alcoholism, poor parental care, poverty, poor living conditions, poor health, accidents and traumas, school bullying, recurrent physical punishment, physical, sexual and emotional abuse in- and outside the family, severe burden/ serious concerns, attempted suicide, attempted rape, leaving home for several days without telling anyone, committed suicide or suicide attempt of a close relative. The events were recorded dichotomously, present or not present during lifetime, and were then counted to form the total number of adverse life events. On the bases of the percentile distribution (25-50-25) the subjects were divided into groups with minimal (0-1 events), moderate (2–5 events) and frequent (6–18 events) history of stressful life events.

3.2.13. Smoking habits (Paper I)

Four levels of smoking were defined based on self-administered questionnaires: 1) never tried smoking, 2) have tried but currently not smoking, 3) irregular smoking (up to twice a week) and 4) regular smoking (smoking every day or

almost every day). Since tobacco smoking has been shown to inhibit platelet MAO activity (Fowler et al., 1996), these data were included to the relevant analyses.

3.2.14. Measurement of platelet MAO activity (Paper I)

Platelet MAO activity was measured in both cohorts of the ECPBHS sample. Venous blood samples were collected into 4.5-ml test tubes containing K3EDTA as an anticoagulant. Platelet MAO activity was analysed in platelet-rich plasma by a radioenzymatic method with [^{14}C]-β-phenylethylamine (β-PEA) ("Amersham") as the substrate according to the procedure described by Hallman et al. (1987) after modification by Harro et al. (2001). Blood samples were collected by antecubital venipuncture into 4.5 ml Vacutainer® tubes containing DTA as an anticoagulant. The samples were centrifuged for 10 min with 800 rpm, obtaining platelet-rich plasma. Part of the obtained plasma (200 µl) was used for counting platelets in certified laboratories. One ml of platelet-rich plasma was stored at –80˚C until the measurement of MAO activity. After melting the platelet-rich plasma on ice, platelets were sonicated with Bandelin Sonopuls Ultrasonic Homogenizer HD2070 4 x 10 s with intervals of 5 s at 4˚C. Then 40 µl of 0.1 mM [^{14}C]-β-PEA was mixed with 50 µl of sonicated plasma, followed by 4 min incubation in 37˚C water bath. After that, 30 µl of 1.0 M HCl was added to stop the reaction and all the tubes were put onto an ice bath for another 10 minutes. After adding 750 µl solution of toluene and ethylacetate (1:1), all the samples were mixed on a shaker (Vibromax 110, Heidolph) for 30 s at 1700 rpm, and thereafter centrifuged for 5 min at 2000 rpm. From the organic phase 500 µl was pipetted into vials with 8 ml of scincillation liquid (Optiphase "HiSafe"3, Wallac). For standard samples 50 µl of 0.1 mM mM [^{14}C]-β-PEA was added to 8 ml of scincillation cocktail. All the samples were analysed in duplicate and blindly and corrected using a reference sample. Radioactivity was measured in a β-counter (Wallac Guardian 1414 Liquid Scincillation Counter). MAO activity was calculated using the following formula: [the amount of the substrate (nmol) x β-count of the sample (cpm) x 1.5]/[β-count of the standard (cpm) x incubation time (min) x the count of platelets in 50 µl of platelet-rich plasma (10^{10} of platelets)] and expressed as nmol of substrate oxidized per 10^{10} platelets per min (nmol x min^{-1} x10^{10} platelets^{-1}).

3.2.15. Genotyping of the 5-HTTLPR (Papers I, II, III, IV)

In the population-based sample the genotyping was carried out as described above.The alleles at the 5-HTTLPR locus were amplified from genomic DNA using polymerase chain reaction (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 labeled with a 5'-FAM. Reagents and conditions for the PCR reaction were: 1x 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 95ºC, followed by 35 cycles with 30 s at 95ºC, 30 s at 59ºC, 30 s at 72ºC, and ended with 10 min at 72ºC. PCR products were then run on an ABI 3100 Genetic analyzer (Applied Biosystems), and scored using the software GeneMapper 1.5 (SoftGenetics). All genotypes were manually checked on chromatograms to detect inconsistencies, and where needed, amplified and scored the second time. Genotype frequencies were distributed in Hardy-Weinberg equilibrium.

In the patient sample the modification of the method by Anchordoquy et al. (2003) was used. The primers were: Forward: 5'-6FAM-ATG CCA GCA CCT AAC CCC TAA TGT-3', Reverse: 5'-GGA CCG CAA GGT GGG CGG GA-3'. Amplification was conducted in total volume of 20 µl. PCR reaction components and final concentration were as follows: 1 x of 5x HotFirepol BLEND with BSA 2.5mM $MgCl_2$ (Solis Biodyne); 5% of DMSO; 1 x of 10xSolution S (Solis Biodyne); 380 µM each of the forward and reverse primers; 10–50 ng of template DNA. The touchdown PCR cycles were used as by Anchordoquy et al, 2003. The electrophoresis was made on ABI PRISM 3130XL genetic analyzer 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 GeneMapper V.4.0 software. Genotype frequencies were distributed in Hardy-Weinberg equilibrium.

3.2.16. Genotyping of the BDNF Val66Met polymorphism (Paper V)

The genomic DNA was extracted from venous blood and all ECPBHS participants who had donated blood samples were successfully genotyped for the BDNF Val66Met (SNP rs6265). Genotyping was carried out using two methods: restriction analysis as the main method and sequencing reactions for lower quality DNA (one fifth of the samples). 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 a Biometra UNO II thermal cycler. PCR reaction components and final concentrations were as follows: 1:10 tartrazine buffer (750 mM Tris-HCl pH 8.8, 200 mM $(NH)_2SO_4$, 0.1% Triton × 100, 5% Ficoll 400, 10 mM tartrazine); 1.9 mM $MgCl_2$; 0.1mM 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'; 1.5 U Taq DNA polymerase (FIREPol). To determine 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 20 s at 96°C,

15 s at 50°C, 40 s at 72°C, and final extension of 6 min at 72°C. PCR products were visualized in 2% agarose gel electrophoresis with ethidium bromide.

For restriction analysis 0.3 U of restriction enzyme Hin1II; 1.6 µl buffer G and 0.34 µl distilled water was added to PCR product, then incubated overnight at 37°C and electrophoresed on 3% agarose gel stained with ethidium bromide. Dideoxy sequencing was carried out with Applied Biosystems BigDye® v.3.1 Kit. Sequencing reactions were performed in a total volume of 10 µl and reaction components were as follows: 1.6 pmol/µl primer R 5'-ATA CTG TCA CAC ACG CTC-3'; 2 µl buffer BigDye® Terminator v1.1,v31.1; 0.7 µl BigDye® Terminator v3.1 Ready Reaction Mix and 1 µl of PCR product. DYE sequencing reaction conditions consisted of 30 cycles of 95°C for 15 s, 50°C for 10 s and 60°C for 45 s. The product in total volume 10 µl was precipitated at –20°C for 30 min using 1 µl 7.5 M ammonium acetate, 1 µl red dextran (10 mg/ml) and 30 µl of cold 96% ethanol. After centrifugation and washing with 70% ethanol, DNA was suspended in 10 µl of 70% formamide and sequenced by AB 3730xl Sequencer. Results were analyzed using ChromasPro v.1.34 software.

Hardy-Weinberg equilibrium test was performed with the HelixTree software package (Golden Helix, Inc. MT, USA). Genotype frequencies were distributed in Hardy-Weinberg equilibrium ($\chi 2=1.11$, $p = 0.29$).

3.3. Data analysis

Statistical analyses were carried out using Statistica version 7.0 software. Associations between the test scores and genotype were assessed by one-way analysis of variance (ANOVA). Interaction effects between the genotype×group were assessed by two-way ANOVA. For comparison of the groups Bonferroni *post hoc* **(Papers II and III)** and Fisher LSD *post hoc* **(Papers I, IV and V)** analyses were used. Covariation analysis was used to control the effect of a third variable. In power calculations the value of alpha was set to 0.05, and the effect size was based on regression coefficient **(Paper V)**. Self-reported measures were standardised into *z*-scores indicating how far and in what direction the group deviates from the whole sample's mean expressed in units of its distribution's standard deviation (SD), according to the formula $Z_X=X-M_X/SD_X$, where Z_X accounts for the z-score, X for personality measure's score, M for the sample's mean and SD for standard deviation of the mean (**Papers I, II, IV and V**).

4. RESULTS AND DISCUSSION

4.1. The prevalence of eating disorders and related symptoms

4.1.1. The use of weight control methods among adolescents (Paper V)

The analysis of the use of weight control methods is based on data collected during the second follow-ups. It was found that among 15–18 years old girls, 51.4% had made attempts to decrease their body weight either by dieting, restriction of meal sizes, training, reducing meal frequency or starvation. Only 11.8% of the boys had made attempts to decrease their body weight, and the most prevalent method was physical training. When the participants' actual energy intake was compared, the girls who had reported having made attempts to decrease their body weight were found to consume less calories per day as compared to the nonregulating group, validating their reports on behaviour. In boys there was no difference in energy intake between the subjects regulating vs not regulating their body weight. The attempts to decrease body weight were associated to drive for thinness and bulimia in girls (**Table 1, Paper V**).

The high prevalence of dieting and other weight control methods among girls suggests that this may be a risk period where heightened importance has been placed on thin ideal and desired body image. As compared to adolescent girls, the incidence of dieting and fasting among adolescent boys has been found to be quite low also in other studies. The boys are more likely to employ exercise to control their body weight rather than alter their eating patterns (Drewnowski et al, 1995; McCabe & Ricciardelli, 2003).

Since dieting heightens the risk for eating disorders, understanding the presence of weight control methods in the general population may be helpful in designing the prevention programs.

4.1.2. The prevalence of eating disorders

Based on DSM-IV diagnostic criteria the following ED classification was used: BN purging type (BN-P), binge eating disorder (BED), anorexia nervosa restricting type (AN-R) and eating disorders not otherwise specified (EDNOS). Subjects with EDNOS were those who had either subthreshold AN (all of the criteria for AN were met except that the individual had regular menses, or the low weight criterion for AN not met), subthreshold BN (binge eating and inappropriate compensatory behaviours at normal weight, but not meeting the frequency criterion for BN), or inappropriate compensatory behaviours in the absence of binge eating.

Overall 7.7% of women and 1% of men had an eating disorder. The current prevalence of ED in women was 0.7% for AN-R, 1.4% for BN-P, 1.8% for BED and 3.8% for EDNOS, and in men 0.5% for BED, and 0.5% for EDNOS. There were no individuals with AN binge-purge type or BN non-purging type among women. No AN or BN cases were found in men.

These results confirm the substantial prevalence of ED in early adulthood, which is in concordance with other epidemiological data (Hudson et al., 2007; Preti et al., 2009). It should be noted however that diagnostical data in our study was based on screening questions rather than full clinical assessment. The male-to female ratio was 1:8 which is lower than those reported in clinical case surveys (Hoek and Van Hoeken, 2003) but in the same range with population-based data. Given the fact that the prevalence of nonpurging BN is rather low, it is not surprising that it was not found in our sample. However, in the EDNOS group there were few women with subthreshold BN who did not have the purging behaviour. Since all women with AN were of restrictive type there is a possibility that the purging behaviour was not reported by participants, it is known that the minimisation of symptoms is often concurrent with AN. The peak period of risk for onset of ED has been reported to be between 17 and 18 years (Stice et al., 2009), thus our sample was representative of sensitive age group.

4.2. The association of eating disorder symptoms with the biomarkers of the serotonin system

4.2.1. The 5-HTTLPR, symptoms of eating disorders and symptom severity (Paper I, II, IV)

To test the associations between test scores and the 5-HTTLPR genotype the participants were divided into two groups based on whether they were carrying the *s*-allele or were homozygous for the *l*-allele. The 5-HTTLPR allelic variations were not independently associated with drive for thinness or bulimia scores (**Paper I, II, IV**).

There is limited data available on the effect of the 5-HTTLPR allelic variants on drive for thinness. While Frieling et al. (2006) reported the effect of the *s*-allele on drive for thinness, the other studies conducted in presumably healthy subjects to test the effect of the 5-HTTLPR have not found such an effect on dietary restraint or drive for thinness (Racine et al., 2009; Matsushita et al., 2002). As mentioned previously, in most of the studies conducted in ED patients the effect of the allelic variations on ED symptoms has not been found (Hinney et al., 1997; Sundaramurthy et al., 2000; Lauzurica et al., 2003; Steiger et al., 2005b).

The 5-HTTLPR genotype effect on binge eating and drive for thinness was not observed even after the covarying effect of impulsivity and anxiety was controlled for (**Paper II**). This result is in line with the study conducted by Racine et al. (2009) who also found no evidence to suggest that impulsivity moderates the association between binge eating and the 5-HTTLPR allelic variations. There is a possibility that different aspects of impulsivity which are not assessed by BIS-11 may moderate this relationship. It has been reported that binge eating is associated with alleviation of negative affect (Fischer et al., 2003; Claes et al., 2005), and similarly, the urgency or tendency to act rushly when experiencing negative affect has been shown to predict eating disorders (Whiteside et al., 2005). Indeed, the *s*-allele of the 5-HTTLPR is associated with increased affective dysregulation but not directly to binge eating in BN patients (Steiger et al., 2005). We observed the similar effect in the population-based sample where in the binge eating group women carrying the *s*-allele showed significantly higher levels of bulimia scores as compared to the binge-eaters homozygous for the *l*-allele and to the control group (**Fig 1**).

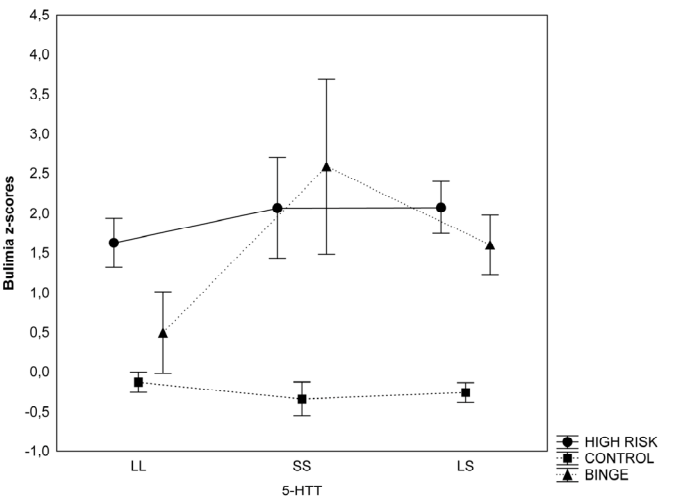

Figure 1. *Z*-scores of EDI-2 bulimia subscale in relation to diagnoses and 5-HTTLPR genotype. Vertical bars denote 0.95 confidence intervals.
Note: HIGH RISK, high risk for binge eating; BINGE, binge eating group

Moreover, in the binge eating group and in the high risk group for binge eating, women with *s/s* genotype had also higher levels of state anxiety (**Fig 2**) and tendency for higher impulsivity (**Fig 3**), referring to comorbid anxiety and poor response inhibition (**Paper II**). These data show that while the 5-HTTLPR genotype does not predict symptoms of binge eating, the *s*-allele, and especially the *s/s* genotype increases the risk for affective instability and symptom severity.

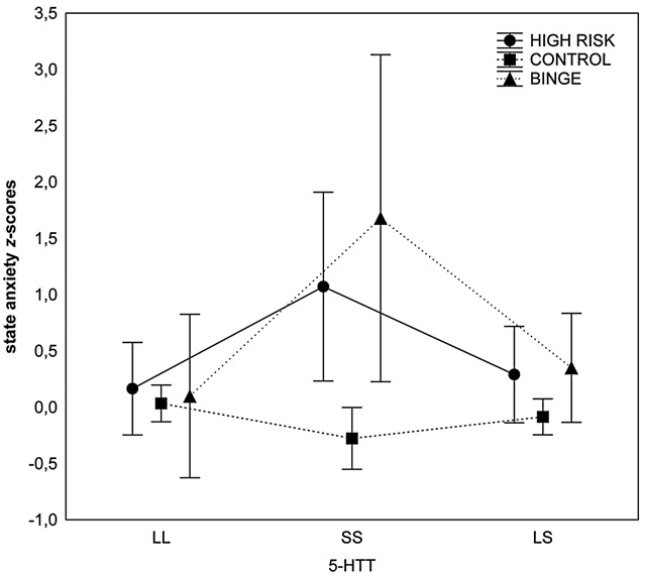

Figure 2. *Z*-scores of STAI-2 state anxiety in relation to diagnoses and 5-HTTLPR genotype. Vertical bars denote 0.95 confidence intervals.
Note: HIGH RISK, high risk for binge eating; BINGE, binge eating group

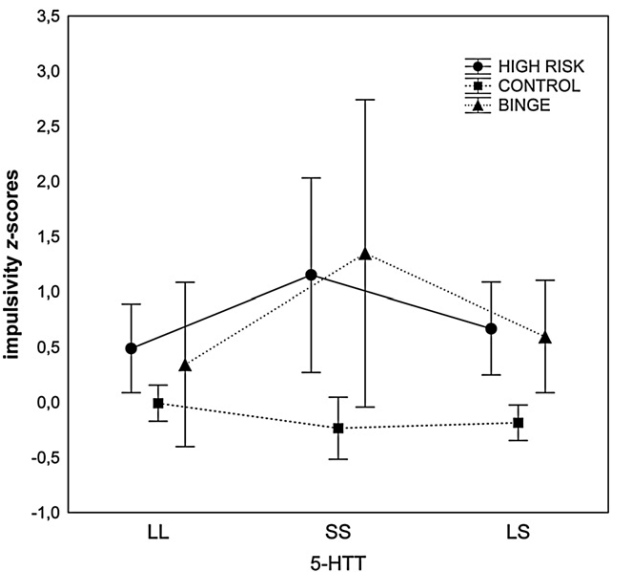

Figure 3. *Z*-scores of BIS-11 subscale in relation to diagnoses and 5-HTTLPR genotype. Vertical bars denote 0.95 confidence intervals.
Note: HIGH RISK, high risk for binge eating; BINGE, binge eating group

The role of emotion in disposition to rash action is present in several trait models (Gray, 1990; Watson & Clark, 1993). Individuals with high levels of both anxiety and impulsivity show emotional lability, emotional intensity, and high rates of impulsive acts (Patterson & Newman, 1993). Ecological momentary assessment has indicated that ED individuals are more likely to binge when experiencing negative mood states (Engel et al., 2007). Thus, it could be suggested that the *s*-allele carriers are more likely to regulate their anxiety or other negative affects by reckless actions like binge eating, and while the latter alleviates negative affect, this further maintains the disordered eating once it has started.

Our results also suggest that individuals homozygous for the 5-HTTLPR *l*-allele do not develop severe binge eating even if they occasionally binge, possibly because of higher emotional stability. In fact, there is evidence that the *l*/*l* genotype reduces emotional reactivity (Champoux et al., 2002) and is associated to shyness and behavioural inhibition (Yirmiya et al., 2001; Arbelle et al., 2005). This is also supported by data showing that the *l*/*l* homozygotes have hypoactive limbic responses as compared to the *s*-allele carriers (Hariri et al., 2002; Pezawas et al., 2005).

4.2.2. Platelet MAO activity, the 5-HTTLPR and symptoms of eating disorders (Paper I)

In this study cross-sectional associations between platelet MAO activity, the 5-HTTLPR and disturbed eating behaviour were studied in adolescent girls and boys (**Paper I**). Since low platelet MAO activity is considered to be a biological marker of vulnerability for disinhibition, and is repeatedly shown to be associated with high impulsivity (Oreland et al., 2002), low platelet MAO activity was expected to be associated with binge eating. Platelet MAO activity was not independently associated with binge eating or drive for thinness though. Although the presence of the *s*-allele in combination with low platelet MAO activity has been associated with self-reported impulsivity (Paaver et al., 2007) the interactive effect of platelet MAO activity and the 5-HTTLPR on binge eating was not observed. However, when the participants were divided by the lower and higher quartile values of platelet MAO activity into a low, medium, and high platelet MAO activity group (**Table 1, Paper I**) an interaction effect between the 5-HTTLPR genotype and platelet MAO activity was observed. Interestingly, individuals homozygous for the 5-HTTLPR *l*-allele and with high platelet MAO activity exhibited higher scores on drive for thinness as compared to the other groups **(Fig 4)**.

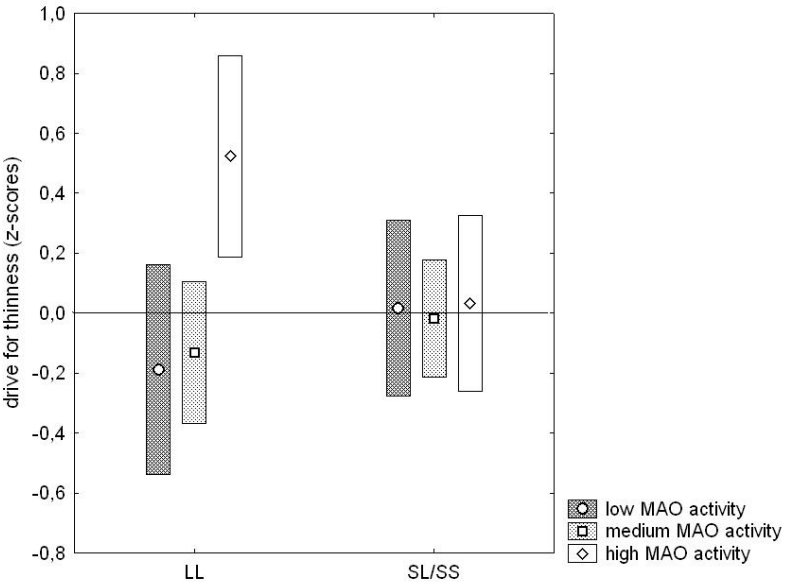

Figure 4. Z-scores of EDI-2 drive for thinness subscale in the 5-HTTLPR short allele carriers (*sl/ss*) and the homozygotes for the long allele (*ll*) with low, medium, and high platelet MAO activity. Vertical bars denote 0.95 confidence intervals.

The results suggest that the preoccupation with dieting and weight gain is the highest in girls with the presence of two markers of higher serotonergic capacity. This may refer to a subgroup of people with eating disturbances who are markedly anxious, rigid and exhibit obsessive-compulsive traits. This suggestion is supported by studies conducted in anxiety disorders patients, where high platelet MAO activity has been reported to associate with high levels of anxiety and OCD (Irving, 1989; Swedo et al., 1992; Cath, 2001). The latter has also been associated to the 5-HTTLPR *l/l* genotype (Bengel et al., 1999; Baca-García et al., 2005; Hu et al., 2006; Dickel et al., 2007). OCD is one of the most prevalent comorbid disorders in ED patients (Godart et al., 2003; Kaye, et al., 2004) and the features of OCPD and ED have been reported to share a common familial cause (Lilenfeld et al., 1998; Lilenfeld et al., 2000). Since anxious and obsessive symptoms have their onset in childhood before the appearance of ED symptoms (Anderluch et al., 2003; Kaye et al., 2004), it is possible that these traits create a susceptibility to the development of an ED.

4.2.3. The effect of the 5-HTTLPR on compulsiveness related traits in eating disorders patients (Paper III)

In this study it was further investigated whether the ED patients can be characterised by obsessive-compulsive traits independent of the clinical subtypes, and whether allelic differences in the 5-HTTLPR are associated with these traits. The group differences in eating disorder symptoms and perfectionism components are given in **Table 2, Paper III**.

The most notable differences in perfectionism subscales emerged in concern over mistakes and personal standards where both the binge and the restrictive group scored higher than the control group but there were no differences between the eating disorder groups themselves. This supports the previous results showing that ED patients can be characterised by perfectionistic traits but BN, BED and AN patients do not differ in this respect (Pratt et al., 2001; Castro-Fornieles et al., 2007). There was a significant genotype×group interaction effect on preoccupation with body image and body weight scores, both in the binge and the restrictive group *l/l* homozygotes exhibited higher scores on preoccupation subscale as compared to the *s*-allele carriers (**Fig 5**). Similar tendency was observed in the concern over mistakes subscale (**Fig 6**), though it was not statistically significant unless the patients were merged into one group (**Paper III)**.

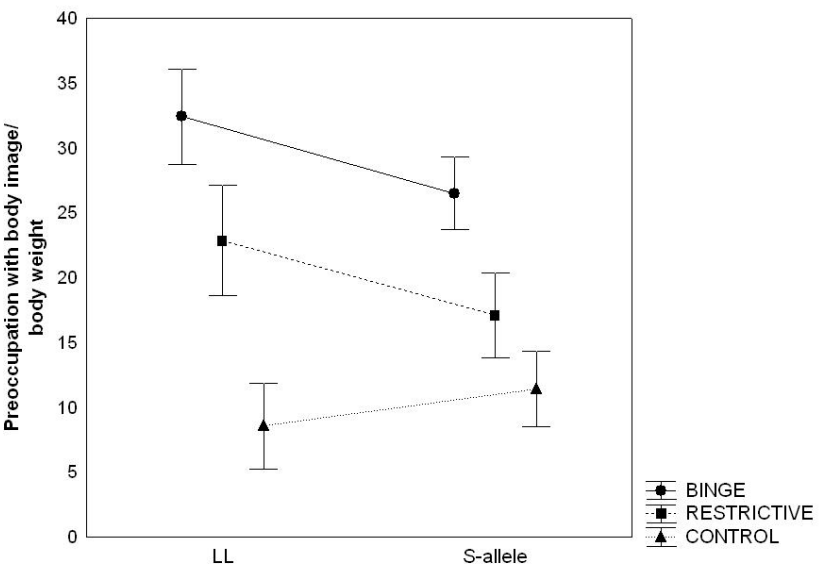

Figure 5. Mean scores of EDAS Preoccupation with body image and body weight subscale in relation to diagnoses in the 5-HTTLPR *l/l* homozygotes vs *s*-allele carriers. Vertical bars denote 0.95 confidence intervals.
Note: BINGE – binge eating group; RESTRICTIVE – restrictive eating group

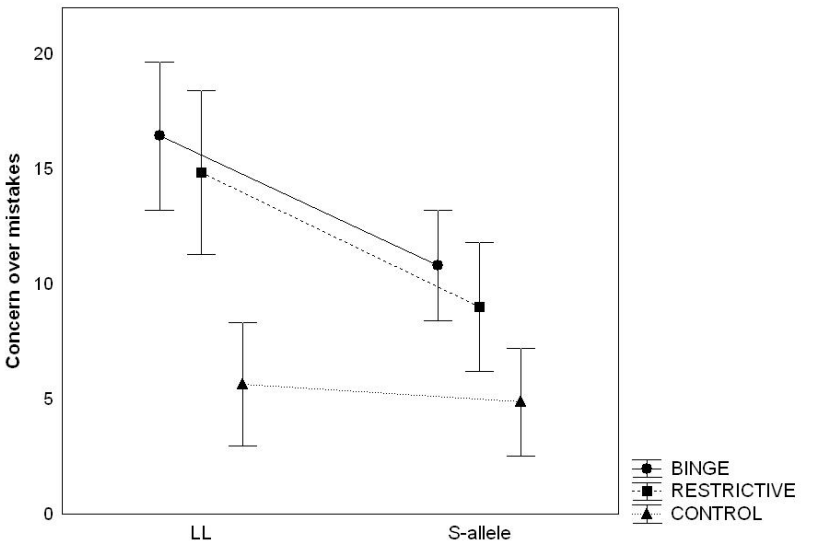

Figure 6. Mean scores of EMPS Concern over mistake subscale in relation to diagnoses in the 5-HTTLPR *l/l* homozygotes vs *s*-allele carriers. Vertical bars denote 0.95 confidence intervals.
Note: BINGE – binge eating group; RESTRICTIVE – restrictive eating group

Concern over mistakes has been considered a maladaptive component of perfectionism most strongly associated to psychological distress (Bieling et al., 2004). In a population-based sample, concern over mistakes has been found to be elevated in individuals with ED as compared to other psychiatric conditions like major depression, alcohol dependence, panic disorder and generalized anxiety disorder (Bulik et al., 2003). Concern over mistakes is one of the most characteristic traits in OCD (Frost & Steketee, 1997) and OCPD patients (Halmi et al., 2005). This suggests that high concern over mistakes in ED group indicates also their higher obsessive trait.

Although it is yet not known which genetic factors increase the risk of developing eating disorders, personality traits like perfectionism and obsessive-compulsiveness, showing a genetic component, could influence the susceptibility to cognitive inflexibility in ED patients. Using the set-shifting paradigm, rigid and obsessive behaviour has been shown to be present in ED patients (Roberts et al., 2007). The results of this study refer to the possible cognitive mechanism of maintenance of symptoms in ED patients with *l/l* genotype. When individuals with this genotype develop beliefs of the over-evaluation of body appearance and eating control then due to their cognitive inflexibility they may be easily locked in cycles of repetitive concerns over body weight, eating, and their meaning for personal life. A further mechanism contributes to problem maintenance. The high concern over mistakes indicates the tendency to follow rigid rules and behaviour patterns for eating and weight control which maintains

the rest of the ED symptomatology. This may partly explain the finding that perfectionism impedes the treatment of ED (Steinhausen, 2002) and suggests that this subgroup of ED patients requires treatment approach tailored to obsessive-compulsive personality traits.

4.2.4. The influence of the 5-HTTLPR × adverse life events on binge eating (Paper IV)

Adverse life events, such as physical neglect, maladaptive parenting behaviours, socioeconomic variables and sexual abuse during childhood, have been shown to predict weight fluctuations and dietary restraint, as well as eating disorders during adolescence or early adulthood in a community based sample (Johnson et al., 2002). In this study it was found that the effect of the adverse life events on binge eating was moderated by the 5-HTTLPR. Individuals with the *s*-allele who by age 15 had reported history of frequent adverse life events were binge eating more at age 18 (**Fig 7**). The effect of the *s*-allele on binge eating was even more pronounced when solely the experience of sexual abuse was considered (**Fig 8**).

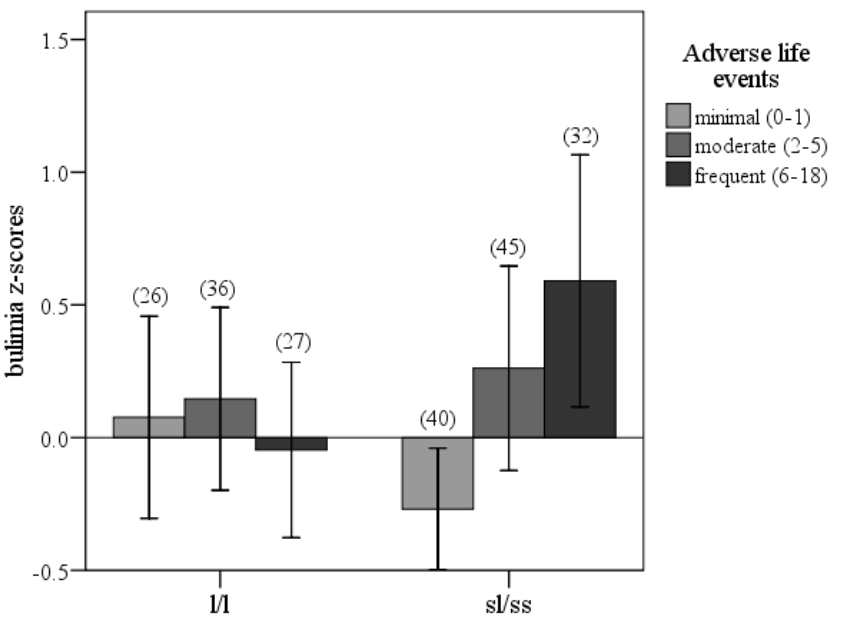

Figure 7. The effect of adverse life events and the 5-HTTLPR genotype on binge eating (presented as EDI-2 bulimia *z*-scores). Vertical bars denote 0.95 confidence interval.

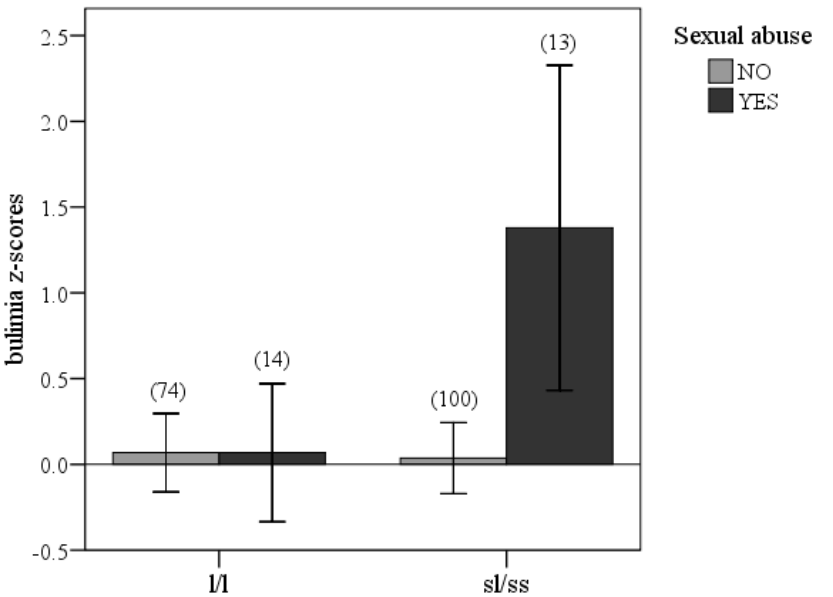

Figure 8. The effect of sexual abuse and the 5-HTTLPR genotype on binge eating (presented as EDI-2 bulimia *z*-scores). Vertical bars denote 0.95 confidence intervals.

There is limited data available on the gene-environment effects in eating disorder patients. Steiger et al. (2004) reported that BN patients with reduced platelet paroxetine binding (as compared to those with higher binding) had experienced more likely childhood sexual abuse, indicating a coincidence of traumatic experiences with hyposerotonergic tendencies in adult women with eating disorders. The authors argue that childhood abuse may contribute to lasting sensitivities of the 5-HT system and in that case such effects might heighten susceptibility to serotonergic dysregulation following stress or negative affects that may influence the 5-HT system.

Several lines of evidence suggest that serotonin plays a role in regulating HPA axis activity. Serotonergic systems can either facilitate or inhibit HPA axis activity and stress related physiological or behavioural responses (Lowry, 2002). Functional studies of the raphe nucleus and serotonergic projections arising from it have suggested that serotonergic systems within the raphe nucleus contribute to resistance, tolerance and coping responses with the acute or chronic stress (Deakin, 1996). 5-HTT gene knock-out mice have been found to exhibit increased HPA axis in response to acute stress (Li et al., 1999). Recently it was reported that girls homozygous for the *s*-allele produce higher and prolonged levels of cortisol in response to stress than *l*-allele carriers, indicating that the 5-HTT gene variation affects HPA axis activity (Gotlib et al., 2008). Similar lines of evidence come from animal research. Among infant rhesus macaques the *s*-allele carriers had higher levels of adrenocorticotropic

hormone in response to maternal separation than did *l/l* homozygotes (Barr et al., 2004; McCormack et al., 2009).

It has been suggested that abnormalities in the response mechanisms to stress and in the HPA axis functioning could explain the association between traumatic childhood events and eating disorders (Basurte et al., 2004). While the *s*-allele carriers may be biologically more reactive to stress related stimuli, then in eating disorders patients this may manifest in more severe binge eating. Activation of the HPA axis under conditions of chronic stress tends to heighten the more prolonged central actions of glycocorticoids in the orexigenic appetite centers (Kyrou & Tsigos, 2007).

The inconsistent results of the association between the 5-HTTLPR and eating disorder symptoms may be because participant`s history of adverse life events has not been considered in these studies. The findings of the present study need to be replicated and ideally objective methods of environmental adversity should be used. Also, gene×gene×environment interactions could probably explain larger variability in binge eating in response to adverse life events since it is unlikely that the 5-HTTLPR interacts with environmental factors entirely independently of other genes.

4.2.5. The effect of the BDNF Val66Met genotype × food restriction on binge eating (Paper V)

The met-allele of the BDNF Val66Met polymorphism has been associated with eating disorders, but the underlying mechanism of its contribution is not known. In this study it was examined whether the effect of the BDNF Val66Met polymorphism on binge eating and drive for thinness is dependent on food restriction. The results showed that among adolescent girls, the BDNF met-allele carriers who practiced the most extreme weight control behaviours like reducing their meal frequency and/or starvation, which was also validated by their reduced caloric intake, were more engaged in binge eating. This interaction effect was not found in boys, which could be explained by the low prevalence of food restriction as a weight control method.

The dietary restraint model of eating disorders asserts that calorie restriction increases the risk for binge eating and bulimia nervosa (Polivy & Herman, 1985). The girls reporting to attempt to lose their weight had indeed higher scores in bulimia subscale, but the mean score was clearly below the suggested cut-off point for this subscale (**Table 1, Paper V**). Although food restriction has the effect on binge eating even within the low range of signs of disturbed eating behaviour, the results of this study show that the BDNF Val66Met polymorphism moderates the association between food restriction and binge eating, and that the met-allele carriers are more affected by the effect of food restriction on binge eating as compared to val/val individuals. Interestingly, the more extreme the food restriction, the more prone the BDNF met-allele carriers were to binge eating (**Fig 9 and Fig 10**).

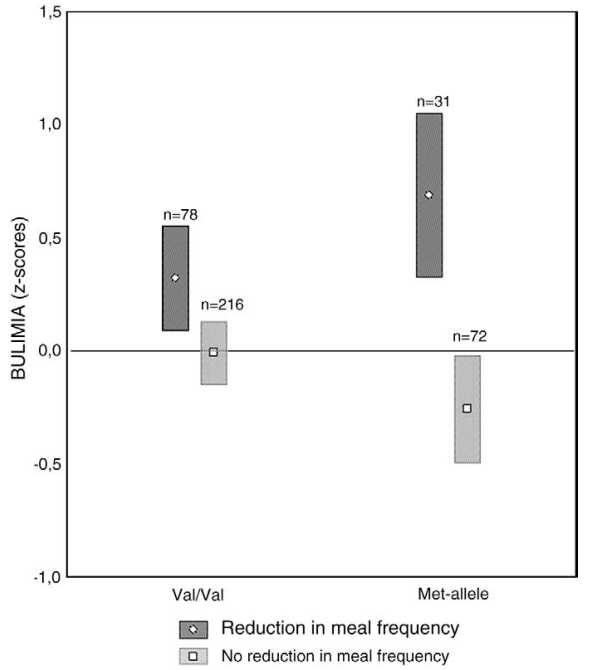

Figure 9. *Z*-scores of EDI-2 Bulimia subscale in relation to food restriction (reduction in meal frequency) in BDNF val/val genotype vs met-allele carriers. Vertical bars denote 0.95 confidence intervals.

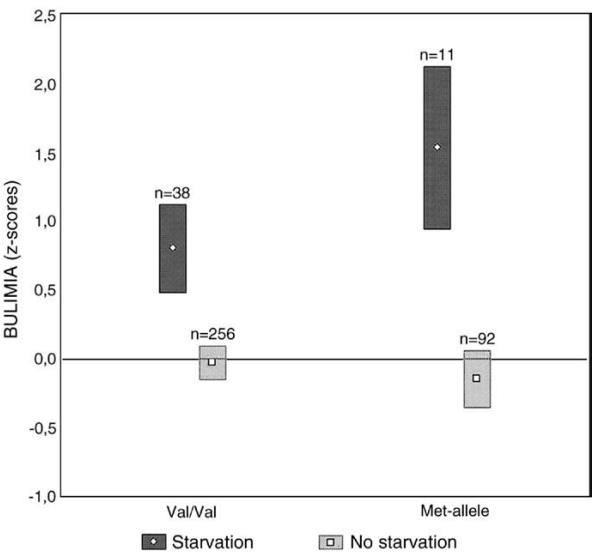

Figure 10. *Z*-scores of EDI-2 Bulimia subscale in relation to food restriction (starvation) in BDNF val/val genotype vs met-allele carriers. Vertical bars denote 0.95 confidence intervals.

It has been found that the met-allele carriers show a stronger reaction to emotional stimuli (Montag et al., 2008) and are more sensitive to reward dependence than val/val subjects (Itoh et al., 2004). Binge eating has been also shown to be related to increased reward sensitivity and the inability to delay gratification (Kane et al., 2004; Davis et al., 2007; Guerrieri et al., 2008). It is possible that the BDNF met-allele has a role in the development of eating disorders because it increases reward dependence, which in subjects who engage in restrictive diets, thus making food a highly rewarding stimulus, enhances their vulnerability to binge eating.

5. CONCLUSIVE REMARKS

Studies indicate that the momentary status of the eating disorder patients represents diverse contributing processes: transient effects of food restriction, effects related to impulsive and compulsive traits, and the effects precipitated by environmental stimuli. In the present thesis it was found that the markers of the serotonin system moderate these effects and may explain the heterogenity in eating disorder symptoms and related traits.

While dieting is a widely practised way to regulate body weight in adolescent girls only a small proportion of these girls develop eating disorders. The results of the present thesis show that the BDNF Val66Met genotype moderates the effect of food restriction on binge eating and suggest that the met-allele carriers of this genotype are especially vulnerable to this effect. This finding may explain why some people develop binge eating in response to dieting and others do not.

The 5-HTTLPR *l/l* genotype was found to be related to preoccupation with dieting and body image, cognitive inflexibility and maladaptive perfectionism in women with eating disorders. A similar effect was observed in the population-based sample of adolescent girls where the high serotonin activity was associated to concern and preoccupation with dieting and weight gain. On the contrary, the *s*-allele carriers show more severe binge eating and especially homozygousity for the *s/s* allele is associated with higher levels of impulsivity and emotional instability in individuals screened positively for binge-type eating disorders and in individuals with high risk for binge eating. Moreover, the *s*-allele carriers were observed to be more sensitive to adverse life events and to show elevated binge eating in response to chronic stress.

In the last decade more attention has been placed to understand underlying biological mechanisms of eating disorders, and it has even argued that diagnostic criteria should possibly reflect underlying biological processes (Bulik et al., 2007). The idea of different eating disorders subtypes that may in addition to personality traits comprise genetic determinants has been elaborated by several researchers (Steiger et al., 2004; Bailer et al., 2007). The results of the present thesis suggest that there may be a subtype of patients who carry the *s*-allele of the 5-HTTLPR, have difficulties in regulating their emotions and behaviour which amplifies susceptibility to binge eating, possibly corresponding to the proposed dysregulated/impulsive subtypes, while homozygosity for the 5-HTTLPR long allele reflects eating disorder individuals characterised by obsessive-compulsive personality traits possibly corresponding to the constricted/compulsive eating disorder subgroup. These findings further suggest that individuals with eating disorders would benefit from a treatment response tailored to the traits characteristic to the patient. Thus, interventions that in addition to dietary restraint target impulse control problems or obsessive preoccupation and constraint, may be more beneficial.

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8. SUMMARY IN ESTONIAN

Serotoniinisüsteemi talitluse biomarkerid ja söömishäirete sümptomid

Söömishäirete keskmeks on püsivad pealetungivad mõtted oma kehakaalust ja -kujust ning tugev hirm kehakaalu tõusu ees, mistõttu tehakse äärmuslikke katseid (näljutamine, range dieet, toidu väljutamine) seda vältida. Söömishäiretega inimestele ei ole omane mitte ainult dieedi pidamine, vaid toitumise piiramisega kaasnev suurenenud enesekontrollitunne ja seeläbi tajutud enesehinnangu paranemine. Toitumise piiramine omakorda suurendab aga ülesöömise riski ning kontrollikaotust söödavate toidukoguste üle. Kuigi dieedipidamine on oluline riskifaktor söömishoogude tekkes, ilmnevad kontrollimatud ülesöömishood ja söömishäired vaid mingil osal inimestest. Nii inimestel kui loomadel on näidatud, et suurenenud serotoniini süsteemi aktiivsus viib söömise piiramiseni ja alanenud serotoniini süsteemi aktiivsus kutsub esile liigsöömist. Samas on söömishäiretega patsientidel läbiviidud uurimused andnud üsna vastuolulisi tulemusi, mis võib tuleneda sellest, et raske on eristada toidu piiramisega kaasnenud serotonergilise aktiivsuse muutusi stabiilsete püsiomadustega kaasnevatest serotoniinisüsteemi eripäradest.

Söömishäireid on seostatud äärmustega impulsiivses käitumises. Mitmed uurimused on näidanud, et osal söömishäiretega patsientidest on võrreldes kogurahvastikuga raskem kontrollida oma emotsioone ja käitumist. Samas on leitud, et söömishäiretega inimesed on perfektsionistlikud ja kompulsiivsed, mis viitab ülemäära kõrgele emotsioonide ja käitumise kontrollile. Nii impulsiivset kui kompulsiivset käitumist on seostatud serotoniinisüsteemi düsfunktsiooniga. Seetõttu on ka oletatud, et serotonergiline aktiivsus seostub söömishäiretega inimestel pigem püsivamate omaduste nagu impulsiivsuse ja kompulsiivsuse kui söömispatoloogiaga.

Käesoleva ajani ei ole söömishäiretega järjekindlalt seostatud ühtegi geeni, ent serotoniini transporteri (5-HTT) geen kui serotoniini ülekande peamine reguleerija on üks tõenäolisemaid kandidaatgeene seletamaks bioloogilist haavatavust söömishäiretele. 5-HTT geeni promootorpiirkonna lühikest geenialleeli (*s*-alleel) on võrreldes pika alleeliga (*l*-alleel) seostatud vähenenud 5-HTT ekspressiooni ning pärsitud serotoniini tagasihaardemehhanismiga. Senised uurimustulemused 5-HTT promootorpiirkonna polümorfismi (5-HTTLPR) ja häirunud söömiskäitumise vahelistest seostest on üsna vastuolulised.

Antud väitekiri püüab vastata küsimusele, kas serotoniinisüsteemi funktsioon seostub otseselt häirunud söömiskäitumisega või pigem impulsiivsuse spektri omaduste kaudu, mis söömissümptomaatikat mõjutavad. Samuti püüab uurida, kas serotoniinisüsteem mõjutab toitumise piiramise ja ülesöömise vahelisi seoseid.

Uurimustesse olid kaasatud Eesti Laste Isiksuse, Käitumise ja Tervise Uuringus (ELIKTU) osalevad indiviidid ja söömishäiretega patsiendid. Käesolevalt puudub Eestis statistika söömishäirete levimuse kohta, mistõttu ELIKTU

raames läbi viidud sõeluuring annab esmakordselt aimu söömishäirete levimusest Eestis. Selgus, et 7,7%-l naistest ja 1%-l meestest esines käesolevalt söömishäire. Samuti ilmnes, et 51,4% teismelistest tüdrukutest püüavad oma kehakaalu alandada kas dieedi pidamise, igapäevaste toidukoguste vähendamise, kehalise aktiivsuse suurendamise, toidukordade arvu vähendamise või nälgimise läbi. Ainult kümnendik samas vanuses poistest pidas vajalikuks oma kehakaalu alandada, ja seda peamiselt treeningu läbi. Üks uuringu tugevusi oli lisaks eneseraporteeritud andmetele ka objektiivsete toitumisandmete kogumine, mis kinnitas, et tüdrukud, kes peavad vajalikuks kehakaalu alandada, seda ka tegelikult teevad, tarbides päevas keskmiselt vähem kaloreid võrreldes tüdrukutega, kes ei pidanud vajalikuks oma kehakaalu reguleerida (**Artikkel V**).

Käesolevates uurimustes ei leitud sarnaselt paljudele teistele uurimustele otsest seost 5-HTT geeni polümorfismi ja söömishäirete sümptomite vahel (**Artiklid I, II ja IV**). Kui aga uurimuses osalejad söömishäire diagnoosi alusel gruppidesse jaotati, siis ilmnes 5-HTTLPR genotüübi efekt ülesöömishoogude intensiivsusele. Söömishäirega naised, kellele on iseloomulikud kontrollimatud ülesöömishood (buliimia, liigsöömishäire) ja kes on *s*-alleeli kandjad, kogevad võrreldes *l*/*l* homosügootidega enam tungi üle süüa ja kontrollimatuid ülesöömishooge. Samasuunaline interaktsiooni efekt ilmnes ka uuritavate impulsiivsusele ja seisundiärevusele, kus nii ülesöömistüüpi häirega kui ka ülesöömise mõttes kõrgesse riskigruppi kuuluvad *s/s* genotüübiga indiviidid said oluliselt kõrgemad skoorid impulsiivsuse ja seisundiärevuse skaaladel (**Artikkel II**). Tulemused näitavad, et kuigi 5-HTTLPR genotüüp ei ennusta ülesöömishoogude teket, siis *s*-alleel, ja eelkõige *s/s* genotüüp suurendab sümptomite tugevust ning emotsiooni ja käitumise regulatsiooni raskusi.

Uurides kahe serotoniini süsteemi markeri, monoamiinide oksüdaasi (MAO) aktiivsuse ja 5-HTTLPR genotüübi koosmõju söömishäirete sümptomaatikale, ilmnes, et tüdrukud, kes on *l/l* homosügoodid ning kel on kõrge MAO aktiivsus, said oluliselt kõrgemad skoorid kõhnuseihaluse alaskaalal (**Artikkel I**). Kõhnuseihalus ehk hõivatus dieedimõtetest on üks peamisi söömishäirete sümptomeid ja anoreksia riskifaktoreid, millega kaasneb sageli kõrge ärevus. Kuna kõrgenenud serotoniini aktiivsust seostatakse ka obsessiiv-kompulsiivse häirega, millele on iseloomulikud pealetükkivad sundmõtted ja -teod, siis võib spekuleerida, et *l*/*l* homosügootsus koos kõrge MAO aktiivsusega peegeldab oma mõtetest liigselt hõivatud ärevaid rigiidseid indiviide, kel on suurenenud risk kõhnuseihaluseks ja seeläbi söömishäire tekkeks.

Antud hüpoteesi testiti söömishäiretega patsientide valimil, ning leiti sarnased tulemused (**Artikkel III**). Sõltumata söömishäire alatüübist (piiravat vs ülesöövat tüüpi) seostus 5-HTTLPR *l/l* genotüüp suurema hõivatusega kehakaalust ja välimusest, ning eksimuste pärast muretsemisega. Mõlemaid kognitiivseid nähtusi seostatakse obsessiiv-kompulsiivsete joontega, mis suurendavad kognitiivset rigiidsust. Antud tulemus võib selgitada, miks *l/l* genotüübiga indiviididel kehakaalu ja -kujuga seonduvate mõtete ilmnemisel need mõtted ei taha taanduda hoides alal rigiidseid reegleid ja probleemset söömiskäitumist. See tulemus võib ka seletada, miks perfektsionism takistab söömishäirete ravi.

Artiklis IV uuriti, kas 5-HTTLPR genotüüp modereerib negatiivsete elusündmuste mõju söömishäire sümptomaatikale. S-alleeli kandlus seostus suurenenud ülesöömisega varases täiskasvanueas, kui indiviidid olid lapsepõlves kogenud keskmisest enam negatiivseid elusündmusi. Antud uurimustulemus on kooskõlas uuringutega, kus *s*-alleeli kandlust seostatakse suurenenud vastuvõtlikkuse ja reaktiivsusega keskkonnast tulevate stiimulite suhtes, mis võib suurendada psüühikahäirete, kaasa arvatud söömishäirete kujunemise riski.

Toitumise piiramise ja ülesöömise vaheliste seoste uurimiseks vaadati aju kasvufaktori (BDNF) geeni Val66Met polümorfismi mõju (**Artikkel V**). BDNF-i peamine funktsioon on reguleerida ajus sünapsite plastilisust. BDNF on kesknärvisüsteemis laialdaselt levinud, muuhulgas leidub seda ka hüpotalamuse tuumades, mis seotud toitumiskäitumisega. BDNF stimuleerib serotoniini neuronite kasvu, sünapsite arvu ja serotoniini käivet hüpotalamuses. Serotoniin omakorda stimuleerib BDNF-i ekspressiooni. BDNF geenis on mitmeid polümorfisme, nende hulgas Val66Met polümorfism, mis põhjustab aminohappe valiini asendamise metioniiniga proBNDF-i molekuli koodonis. Mõned uurimused kliinilisel populatsioonil on näidanud, et met-alleeli kandjatel on suurem risk söömishäirete tekkeks, aga ei osata veel seletada, mis mehhanismi läbi see toimib. Käesolevas uurimuses Val66Met genotüübi üldist mõju söömissümptomaatikale ei leitud. Küll aga ilmnes, et met-alleeli kandjad on tundlikumad toidu piiramisest tulenevate ülesöömishoogude suhtes, see tähendab, et met-alleeli kandjatel, kes oma toitumist äärmuslikult piiravad, esineb rohkem ülesöömishooge.

Söömishäiretega patsientide seisund kujuneb mitmetest vastastikku mõjutavatest protsessidest: toidu piiramisega kaasnevatest mõjudest, impulsiivsete ja kompulsiivsete joonte mõjudest, ja keskkonnast tulenevatest mõjudest. Käesoleva väitekirja tulemustest nähtub, et serotoniinisüsteemi markerid mõjutavad eelmainitud protsesside toimet söömissümptomitele, mis võib selgitada söömishäirete sümptomaatikas ja kaasuvates joontes ilmnevat märkimisväärset heterogeensust.

9. PUBLICATIONS

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Peamised uurimisvaldkonnad: söömihäired ja serotoniinisüsteemi talitluse markerid; vanuselised erinevused söömishäirete riskifaktorites lastel ja noorukitel; söömishäirete hindamine.

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