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„Body mass index and depression related to
serotonin-transporter gene and COMT gene
polymorphisms “

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1 Introduction

According to the World Health Organisation (WHO), depression is affecting about 121 million people worldwide and it is among the leading causes of disability worldwide. “Major depression is a mental disorder that presents with depressed mood, loss of interest or pleasure, feelings of guilt or low self-worth, disturbed sleep or appetite, low energy and poor concentration” [WHO, 2012a].

“By the year 2020, the WHO estimates that major depressive disorder will reach second place of the ranking of DALYs, which means Disability Adjusted Life Years. DALYs represents the sum of years of potential life lost due to premature mortality and the years of productive life lost due to disability” [WHO, 2012a].

Major depression ranks among the leading causes of decreased life quality with an estimated lifetime prevalence of 15 % [DANNLOWSKI et al., 2010] and an heritability ranging from 31 to 42 % [SCHARINGER et al., 2011] reinforcing the social and economic importance of this disease.

In turn, overweight and long-term body weight variability is linked to psychiatric disorders although the direction of causation remains unclear [HASLER et al., 2005; SIMON et al., 2006].

Since the 1980ies occurrence of obesity has more than doubled worldwide and in 2008, 1.5 billion adults were overweight. Although overweight and obesity are preventable the number is still rising, especially in children; leading to elevated risk for cardiovascular diseases and diabetes [WHO, 2012b].

Both, major depressive disorder and obesity are widespread diseases and share in part the same co-morbidities like increased risk of cardiovascular disease. Common symptoms of depression like altered appetite, weight gain, reduced physical activity and therefore increased risk of obesity show the close relationship of these diseases [SIMON et al., 2006, LUPPINO et al., 2010]. Obesity and depression, both show altered eating behaviour, especially increased intake of energy-dense foods which are often high in trans-fatty acids,

which in turn is associated with elevated risk of depression and obesity [WHO, 2012b; SANCHEZ-VILLEGAS et al., 2011]. Although studies confirmed the link between obesity and depression, causality remains bidirectional, meaning that obesity seems to increase the risk of developing depression and in turn depression seems to predict the development of obesity in longitudinal studies [LUPPINO et al., 2010].

On account of these aspects, investigating the molecular and genetic mechanisms of major depression as well as its link to overweight and obesity gets more and more important, has been and is still a big matter of study.

2 Object of research

The idea behind this master thesis is, on the one hand, to investigate whether study participants having experienced depression in the past have a higher body mass index compared to those who never suffered from depression at the time screening. Consequences of depression are for example altered lifestyle with decreased physical activity and changed eating behaviour (e.g. increased intake in high caloric, comfort foods). Those alterations have been shown to result in an increase in body weight. In the first step I used odds ratio calculation to get an overview on how depression affects body weight in the study population.

So the first questions that need to be answered are 1.) “does depression lead to overweight and/or obesity”, 2.) “does mean body mass index differ between healthy, remitted with one former depressive episode and remitted with more than one depressive episode”. In this context, depression related cofactors need to be included into the analysis like gender, age, age at depression onset as well as genetic factors that have been associated with both depression and body weight (serotonin transporter polymorphism rs25531 and Catechol-O-methyltransferase polymorphism rs4680) in the past.

Secondly, it should be tested whether there are mean differences in body mass index accounting for certain personality traits like extraversion, neuroticism,

openness, agreeableness and conscientiousness (personality traits defined by the NEO-Five Factor Inventory). For the analysis subjects were 1.) analysed together because at the time of study recruitment all of them were healthy 2.) divided into groups of healthy, remitted with one former depressive episode and remitted with more than one depressive episode because mean scores of the personality traits assessed by the NEO-FFI might differ between healthy and remitted study participants due to history of depression.

Thirdly, I analysed whether the allele distribution of the two depression related polymorphisms 1.) rs25531 (the serotonin transporter polymorphism of the *SLC6A4* gene) and 2.) rs4680 (*COMT* gene) differs between lean and overweight study participants and if the number of depressive episodes plays a role in this context.

Furthermore I wanted to review the biological relationship between major depression and overweight (elevated body mass index).

3 Background

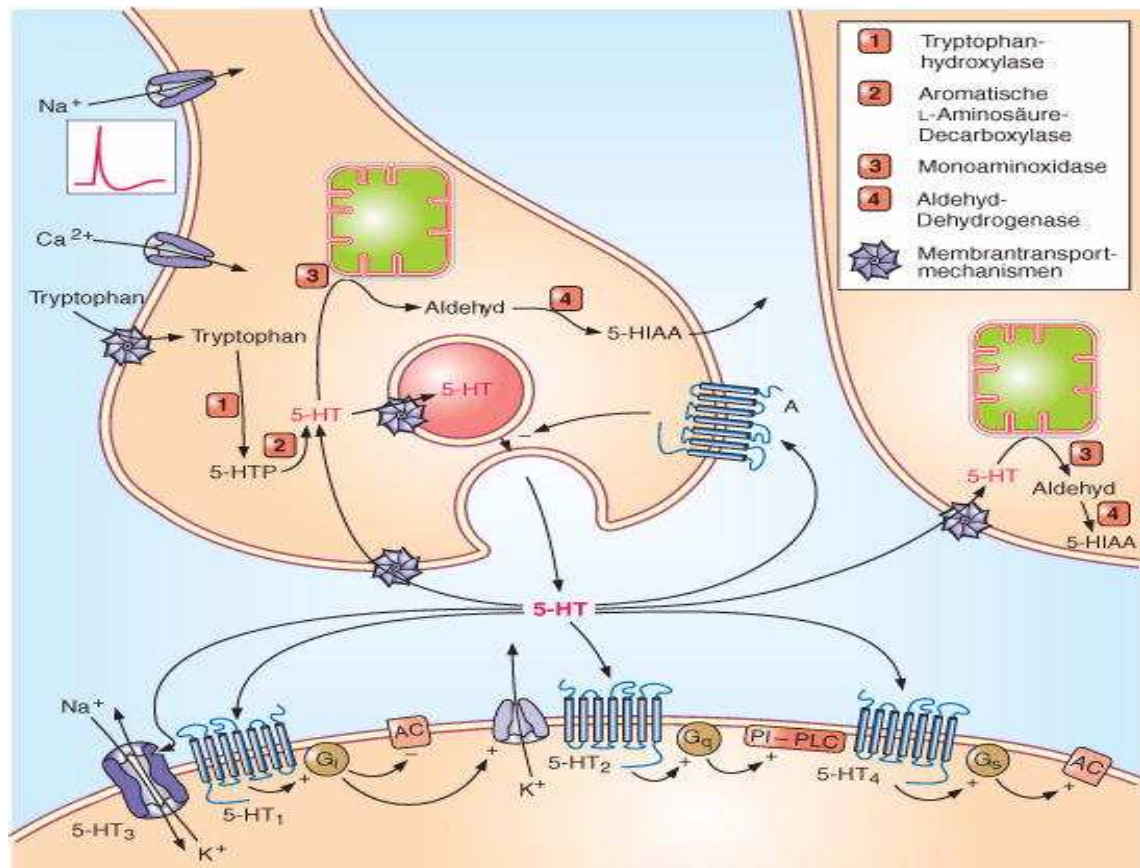
3.1 Aetiology and genetic mechanisms behind MDD

Major depressive disorder is a highly heritable disease and it's multifactorial. Various factors like complex interactions of genes, gene-environment interactions, psycho-social, immunological and neurobiological factors play a crucial role in the aetiology of this disease [PALLADINO, 2009]. Depression phenotypes do not only show disturbances in mood but further impairments of cognitive, motoric, endocrine or autonomic function. Although there has been lots of research, little is known about the aetiology or pathophysiology of depression. The monoaminergic neurotransmitter system has received greatest attention in this context due to the fact that effective antidepressant medications regulate intra-synaptic concentrations of molecules like serotonin [MANJI et al., 2001].

3.1.1 *The monoamine deficiency hypothesis*

The hypothesis that serotonin transmitter systems play a central role in affective disorders emerged after studies showed a decrease in serotonin concentration in different brain regions of suicide victims [HORTON and CATONA, 1991]. The monoamine deficiency hypothesis assumes a dysregulation of neurotransmission mediated by serotonin (5-hydroxytryptamine, 5-HT) released from presynaptic neurons. Serotonin is synthesised from tryptophan by conversion of tryptophan hydroxylase, stored in vesicles in the presynaptic neuron and is then released into the synaptic cleft [BELMARKER and AGAM, 2008]. The serotonin transporter (SERT) is an integral protein in the plasma membrane of the presynaptic neuron and belongs to the SLC6 (solute carrier) gene family of Na^+/Cl^- -dependent neurotransmitter transporters. SERT modulates several functions within the brain such as emotion, cognition, motivation and sleep. After release of 5-HT the serotonin transporter terminates the action of serotonin and recycles it by reuptake. Further, postsynaptic serotonin receptors play a crucial role in major depression. The number of 5-

HT_{1A} receptors has been shown to be elevated in depression and the density of the receptors is decreased in the amygdala of depressed people. Moreover, increased 5-HT₂ receptor activity or up-regulation is associated with depression as receptor up-regulation leads to quick clearance of serotonin from the synaptic cleft and results in a shortened serotonin effect, a correlate for depressive like behaviour [MAES and MELTZER, 2000].



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Figure 1. The picture shows the pathway of 5-HT within the neuron.

The monoamine deficiency hypothesis of depression postulates a lack of the monoamine serotonin in the brain. Serotonin reuptake inhibitors (SSRIs) are common antidepressants which block SERT function hence serotonin action is prolonged in the synaptic cleft which is liable for the antidepressant properties of SSRIs [HAENISCH and BÖNISCH, 2011; BELMARKER and AGAM, 2008].

The primary mechanism of serotonin uptake from the blood plasma is the serotonin transporter on platelets, a saturable mechanism. The molecular mechanisms behind serotonin uptake on both platelets and neurons are very similar. In general, the uptake capacity of serotonin from platelets is proportional to the number of serotonin transporters in the membrane. But the expression of SERT on neurons and glia cells is regulated by the concentration of extracellular 5-HT. *Mercado and Kilic, 2010* report that there is a biphasic mechanism between the serotonin concentration extracellular and the activity of the serotonin transporter. Elevated levels of extracellular 5-HT lead to an initial rise of SERT molecules. This first phase is followed by a drop of SERT below baseline, assuming that in fact high concentrations of extracellular serotonin cause decreased cell surface expression of SERT and therefore limit synaptic availability [MERCADO and KILIC, 2010; KASESS et al., 2013].

Research in the past years has mainly focused on the serotonergic pathways, which contribute to depression and SSRIs are now considered as first-line therapeutics for major depressive disorder but concerns about the effectiveness of these therapies put norepinephrine and dopamine systems more into perspective. Because of the relatively slight efficacy of monoaminergic agents, therapies considering serotonin norepinephrine reuptake inhibitors (SNRIs) and dopamine norepinephrine reuptake inhibitors (DNRI) became more and more attractive [ROBINSON 2007]. Although selective drugs like SSRIs seem to have less side effects, higher tolerability and lower discontinuation rates during treatment than non-selective or dirty drugs (like tricyclic antidepressants (TCAs)), effectiveness is not proven to be better in selective drugs [ANDERSON 2000].

Deriving from tyrosine, dopamine as well as the catecholamines adrenaline and noradrenaline are important neurotransmitters in the central nervous system and recently dopamine has gained attention not only in depression research but also in the field of obesity research. Knowledge of the involvement of dopaminergic reward motivation in obesity has mainly been gained from addiction research.

3.2 The role of the serotonin transporter-linked polymorphic region (5-HTTLPR) in the serotonin transporter gene (*SLC6A4*) in the context of major depressive disorder

There is convincing body of evidence that functional gene variants of the serotonin transporter gene are associated with elevated risk for mood disorders [ZHAO et al., 2006].

The most prominent of those is the 5-HTTLPR length polymorphism mapped on 17q11.1-17q12, a tri-allelic locus with alleles denoted as L_G , L_A and S. [PARSEY et al., 2006; ANCHORDOQUY et al., 2003]. This polymorphism leads to reduction in serotonin reuptake and serotonin transporter binding [ZHAO et al., 2006]; whereas the S allele is associated with reduced availability of the serotonin transporter protein [HOMBERG and LESCH, 2011], slowed down synthesis of the serotonin transporter [ROT et al., 2009] as well as with reduced function of the transporter [HOMBERG and LESCH, 2011]. The less common L_G allele has transcriptional activity comparative to the S allele; therefore they should be analysed together. In contrast, the L_A allele is associated with a higher basal activity of the serotonin transporter as well as with a higher expression level [PARSEY et al., 2006; ANCHORDOQUY et al., 2003].

Comings et al., 1999 reported a heterosis effect for the serotonin transporter polymorphism meaning that heterozygotes show a greater phenotypic effect than homozygotes. In this special context this means that S/S homozygotes should be analysed along with L/S heterozygotes and L_G carriers in L/L homozygotes. These groups need to be compared to L_A carriers [COMINGS et al., 1999].

The a meta-analysis of *Munafò et al., 2008* reported an association between the S allele and a relatively increased risk for depression although this has not been consistently demonstrated across various studies that have been conducted [FURMARK et al., 2008; MUNAFÒ et al., 2008].

Furthermore it is necessary to mention that gene-environment interactions are highly important to explain the susceptibility to mental disorders like major depression. Given that two thirds of the population are S-allele carriers, not every one of them becomes depressed but the polymorphism may influence a persons' sensitivity to certain environmental conditions like for example stress. Stress is a common factor that causes depression, but in turn, not everyone exposed to stress becomes depressed. Genetic layout and stress interact to a greater degree and modulate a person's risk for the development of depression [ROT et al., 2009].

When using neuroimaging techniques like fMRI it can be shown that S allele carriers have relatively increased activation of the amygdala, a brain region regulating and influencing emotions and memory. This is especially true in the context of chronic or severe stress [FURMARK et al., 2008; MUNAFÒ et al., 2008].

3.3 Catechol-O-methyltransferase (COMT) and its link to major depressive disorder

Catechol-O-methyltransferase (COMT) is an intracellular enzyme and catalyses the inactivation of catecholamine neurotransmitters noradrenaline and adrenaline. Both of these catecholamines stimulate depletion of glucose and gluconeogenesis in the liver and skeletal muscles and support lipolysis in fat tissue, leading to a rapid increase in glucose and free fatty acids in the blood; therefore they are highly important for quick energy supply especially in emergencies [MÄNNISTÖ and KAAKKOLA, 1999; LÖFFLER, 2004]. COMT also affects dopamine metabolism and the rs4680 polymorphism in the *COMT* gene has therefore been studied related to diet induced obesity and drug reward. Although there is only one gene for COMT it encodes for two different isoforms of the protein (soluble COMT or S-COMT and membrane bound COMT or MB-COMT). In most human tissues both isoforms can be found whereas in the brain MB-COMT is predominant and located on intracellular

membranes in postsynaptic neurons and glia cells. Regarding that dopamine transporters (DATs) regulate dopamine clearance from the synaptic cleft by reuptake into the postsynaptic neuron – a secondary-active transport and Na^+/Cl^- dependent process – the role of COMT seems to be subsidiary with exception for the prefrontal cortex where expression of DATs is low. Hence, an alternative mechanism for dopamine clearance is needed and COMT is thought to be highly important for prefrontal dopaminergic regulation [MÄNNISTÖ and KAAKKOLA, 1999; MATSUMOTO et al., 2003]. Inhibition of COMT leads to delayed dopamine depletion and thus unfolds an antidepressant effect [KRING et al., 2009; WANG et al., 2007].

A common polymorphism of the human *COMT* gene, located at the chromosome 22q11, is the exon 4 functional variant resulting in a G to A nucleotide transition (Valine to Methionine amino acid transition in the protein). The transition from Val to Met results in a suggested enzyme activity decrease of 67-75 %. Met carriers therefore have lower COMT activity compared to Val homozygotes. Thus reward-related behaviour may be affected by this gene variant, especially the low activity allele (Met) which is related to lower synaptic dopamine levels in the prefrontal cortex [RUIZ-SANZ et al., 2007; WANG et al., 2007; KÄENMÄKI et al., 2010].

The rs4680 polymorphism (Val158Met) is probably the most intensively studied polymorphism in the *COMT* gene and showed associations with reward-related dysfunctions in the brain like obesity, alcoholism and nicotine and heroin addiction. These associations are suggested to be induced by dysregulation of dopamine metabolism. Although there seems to be an association not all studies that have been conducted confirmed this linkage [KRING et al., 2009; WANG et al., 2007; KÄENMÄKI et al., 2010].

As COMT is involved in the estrogen metabolism a gender effect should be taken into account as an alternative mechanism of the associations found because this would enhance environmental effects [WANG et al., 2007; TAMMIMÄKI and MÄNNISTÖ, 2010].

3.5 Depression and its link to body mass index and obesity

Regulation of physiological processes like glucose and energy homeostasis are regulated by serotonin, noradrenaline and dopamine which are likewise important as neurotransmitters in the central nervous system and related to complex mental diseases like depression. Targeting these neural pathways, anti-obesity drugs as well as antidepressants have been tried to be developed. The linkage between body weight and mood can be shown by antidepressants like SSRIs increasing body weight and vice versa by anti-obesity drugs (like Sibutramin/Reductil®) resulting in disturbance of mood [KRING et al., 2009].

The interplay of health behaviour and other environmental factors as well as genetic background may be responsible for the complex underlying pathophysiological mechanisms of obesity and depression and related differential clinical response to anti-obesity and antidepressant drugs [KRING et al., 2009].

Depression and obesity raise public health concerns because of their high prevalence and their increased risk for cardiovascular and other diseases as well as their high prevalence of disability. Although lots of research has been done in this field, the exact relationship between the diseases remains unknown. A meta-analysis of longitudinal studies confirmed that obese people have a 55 % increased risk of developing depression and in turn depressed people's risk of reaching a body mass index in the obese range increased by 58 %. The meta-analysis also showed that the linkage between depression and obesity is stronger than the other way round but highlights that time may play an important role in this context [LUPPINO et al., 2010].

3.5.1 Inflammation as the underlying link

One common biological hypothesis, which might explain the association between depression and obesity is the inflammatory pathway. Obesity and especially excessive abdominal fat is known for its immune system activating properties and therefore for enhancing inflammation. Obesity is also known as a state of chronic subclinical inflammation with increased production of pro-inflammatory cytokines like IL-6, C-reactive protein (CRP) or TNF- α . On the other hand, immune dysregulation seems to play an important role in neurological disorders, especially in Alzheimer's disease, anxiety and depression. Because of its role on both sides, inflammation might be important for understanding the association. [LUPPINO et al., 2010; VON SCHOLTEN et al., 2012; VOGELZANGS].

3.5.2 HPA axis – the joint between depression and obesity

Another attempt might explaining the shared pathophysiological mechanisms behind depression and obesity is the stress axis (HPA axis – hypothalamic-pituitary-adrenocortical axis) [BORNSTEIN et al., 2006]. *Bornstein et al., 2006* report an involvement of dysregulation of the HPA axis in both diseases. While the autonomic nervous system (ANS) reacts immediately to a certain stressor by increasing heart rate and blood pressure, the HPA axis is in charge of mediating long-term stress [ULRICH-LAI and HERMAN, 2009]. *Bornstein et al., 2006* suggested dysregulation of stress or HPA axis for the shared biology of depression and obesity and points out for Cushing's disease as a model of the shared pathophysiological mechanisms of both diseases. In Cushing's disease obesity, insulin resistance, dyslipidemia and hypertension as well as anxiety, psychosis and depression are common whereas the metabolic symptoms are seen as the hallmarks of the metabolic syndrome. HPA axis dysfunction and increased levels of cortisol can also be seen in schizophrenia together with disruption of insulin tolerance and elevated fasting glucose levels [BORNSTEIN et al., 2006; TOALSON et al., 2004].

Although involvement of the HPA axis in obesity seems to be certain, it remains unclear whether weight gain is a result of HPA hyper-activation or either the result of trying to control stress in the way of comfort eating [BORNSTEIN et al., 2006].

3.5.3 How serotonin is involved

Serotonin is known to be involved in eating behaviour and body weight and a study from *Erritzoe et al., 2010* could highlight the importance of the serotonin transporter in this context and report reduced cerebral SERT binding in obese participants. The serotonin transporter gene, which is highly conserved has former been shown to play an important role in obesity. *Murphy and Lesch, 2008* showed that SLC6A4^{-/-} mice become obese which lead to further research and findings pointing to reduced expression rate of the SLC6A4 gene (encoding for SERT) in obese humans. Although clinical data on associations between cerebral serotonin levels (5-HT) and SERT binding are missing, it is supposed that lower cerebral 5-HT levels lead to increased appetite and food intake and the short allele of the rs25531 serotonin transporter polymorphism seems to play a role in this context [ERRITZOE et al. 2010, MURPHY and LESCH, 2008].

3.6 Hunger, satiety and brain function

Regulation of hunger and satiety is very complex and the hypothesis of the ventromedial hypothalamus as a centre for satiety and the lateral hypothalamus as a centre for hunger is out-dated although the hypothalamus remains the central region for energy homeostasis and energy intake and therefore for hunger and satiety [BENOIT et al., 2008]. Signals of hunger and satiety are transported by blood or the neural pathway from the periphery to the hypothalamus. The hypothalamus processes all the incoming information and sends signals of hunger (e.g. hormones like glucocorticoids, cortisol and progesterone or substances like ghrelin, noradrenaline, dopamine,

neuropeptide Y) or satiety (e.g. hormones like leptin and insulin or substances like serotonin and corticotropin-releasing factor (CRF)) [ELMADFA, 2004].

Brain areas regulating energy homeostasis, food intake and satiety are complexly regulated and interconnected. The hypothalamus receives information from amygdala, VTA (ventral tegmental area), orbitofrontal cortex (OFC), NAcc (nucleus accumbens) as well as from leptin, ghrelin, and blood levels of glucose, and free fatty acids. *Erritzoe et al. 2010*, suggested that serotonergic acting components suppress appetite and food consumption when directly administrated to the hypothalamus [ERRITZOE et al., 2010]. The amygdala is responsible for emotional processing of stimuli while NAcc and VTA are responsible for hedonic processing, reward and addiction in this context. The dorsolateral prefrontal cortex receives information from the limbic system (like amygdala, hippocampus, gyrus cinguli) and is in charge of self-control, while the anterior gyrus cinguli is responsible for emotional processing and reward and the hippocampus mirrors learned eating behaviour [KABISCH et al., 2011].

As mentioned above, the hypothalamus is the centre of regulation of hunger and satiety and therefore central when it comes to discuss obesity.

The hypothalamus gathers three very important populations of neurons, so called nuclei; neurons of the arcuate nucleus expresses neuropeptide Y (NPY) and melanocortin receptor (MC-R) antagonist agouti-related protein (AgRP), both stimulating food intake, as well as pro-opiomelanocortin (POMC, precursor of α -MSH) and α -melanocyte-stimulating hormone (α -MSH) and cocaine-and amphetamine-regulated transcript (CART), both inhibiting food intake. Neurons in the paraventricular nucleus are in charge of synthesising food intake limiting (anorexigenic) compounds like corticotrophin-releasing hormone (CRH); in turn, neurons in the lateral hypothalamus produce orexigenic compounds like melanin-concentrating hormone [BENOIT et al., 2008].

Insulin and leptin, both involved in the regulation of food intake too, are able to cross the blood-brain-barrier, suggesting their possibility for central actions and

in fact influence for example POMC expression in the hypothalamus [BENOIT et al., 2008]. This indicates the importance of integrating neuroimaging methods in obesity research. Moreover, brain areas responsible for hedonic behaviour, reward and addiction like the ventral tegmental area (VTA) and nucleus accumbens receive direct signals from hormones like leptin, ghrelin and are altered by metabolic glucose level.

Neuroimaging methods are therefore becoming more and more important in the field of obesity research. In this context, paradigms which examine the brain's response to appetite related stimuli are widely used. Researchers suggest that obesity is associated with altered responses to food stimuli in brain areas related to reward and motivation (striatum and orbitofrontal cortex) as well as emotion and memory (amygdala and hippocampus) because hedonistic drives seem to be more important than homeostatic in the context of modulating food intake [NUMMENMAA et al., 2012; CARNELL et al., 2011; NEARY MT and BATTERHAM RL, 2010].

Studies fiddling with the reward hypothesis are in disagreement whether the alteration of the reward system that affects appetite and overeating is about hypo- or hyper-activation. It remains unclear whether hyper-responsivity of reward related brain structures like insula, orbitofrontal prefrontal cortex, amygdala and striatum to food viewings or either hypo-responsivity which would lead to overeating to balance for this deficiency is the underlying link to overweight and obesity [STICE et al., 2010]. Another theory suggests that reduced dopamine signalling derived from initial overeating leads to hyper-responsivity of the reward circuitry to food and should therefore be linked to obesity [STICE et al., 2011].

4 Methods

4.1 Participants

Patients were invited to the Department of Psychiatry and Psychotherapy, Medical University of Vienna and underwent a clinical diagnostic interview for DSM-IV axis I disorders, medical routine blood tests and electrocardiogram (ECG) recordings after receiving and signing written informed consent [WITTCHEN et al., 1997]. The applied study protocol was approved by the local ethics committees according to the declaration of Helsinki 2008. Recruiting of participants for the study took place at the Medical University of Vienna by displaying recruitment conditions on bulletin boards and by local advertisements.

Assessing previous psychiatric and psychotherapeutic conditions by the German version of the NEO Five-Factor Inventory (NEO-FFI) and the 17-item version of the Hamilton Depression Rating Scale (HAM-D) was performed and data on clinical course and treatment were collected. Eligibility criteria for participation in the study were the following:

- Right handed
- Native german speakers
- Aged between 18 and 45 years
- No medical and/or neurological disorders.

Exclusion criteria according to the study protocol were the following:

- Any psychotropic medication or psychotherapy within the last three months
- HAM-D score above seven
- Any coincidentally or concurrent DSM-IV axis I disorders
- History of schizophrenia, bipolar disorders, substance-related disorders, personality disorders, major depression with psychotic symptoms.

258 participants were divided into 2 general groups. The first group consisted of lifetime healthy controls; the second group was made up of people remitted from major depressive disorder. The second group was again split into remitted patients with one (nDE=1) or more than one depressive episode (nDE>1). In total 260 participants, 112 men and 148 women were included into the analysis.

4.2 Body Mass Index

Body weight and height was available from 258 participants. Therefore the body mass index (BMI) from 110 male and 148 female participants could be calculated by the formula:

$$\text{Body Mass Index} = \text{weight in kilogram} \div (\text{height in meters}^2) \text{ [ELMADFA, 2004]}$$

The body mass index ranges from 15.82 to 35.83 with a mean of 22.5 (± 3.08 standard deviation) within the study population. Split by gender, body mass index ranges from 17.09 to 35.83 with a mean of 23.18 (± 2.72 standard deviation) in males and from 15.82 to 33.06 with a mean of 21.93 (± 3.22 standard deviation) in females.

Participants were divided into four BMI groups (healthy, underweight, overweight, obesity). Classification was made according to the WHO [WHO, 2012c).

Table 1 shows the distribution of the BMI over the four groups:

	BMI-range	Number of males	%	Number of females	%
Healthy	18,5 – 24,99	88	80	112	75.7
Underweight	>18,5	2	1.8	11	7.4
Overweight	25 – 29.99	18	16.4	20	13.5
Obesity	≥ 30	2	1.8	5	3.4

Table 1. BMI range in males and females.

To find out whether the exposure to depression increases body mass index in the study population, a case-control approach was used and odds ratios were calculated. The odds ratio states the chance that an event occurs under the exposition of a certain disease [MCHUGH, 2009]. Because of the probability of a gender effect, the odds ratio for being overweight or obese and a former depressive event was calculated for each gender separately.

Table 2 shows the formula by which the odds ratio can be calculated [MCHUGH, 2009].

	Exposure to depression	No Exposure to depression
Health outcome – overweight or obesity	A	B
No health outcome – healthy BMI	C	D
Odds ratio (OR) = (a/b)*(c/d) or OR= (a x d) / (b x c) [MCHUGH, 2009]		

Table 2. Odds ratio calculation formula.

The standard error (SE) for the natural logarithm of the odds ratio was calculated by the formula:

$$SE = \sqrt{\frac{1}{a} + \frac{1}{b} + \frac{1}{c} + \frac{1}{d}} \text{ [MCHUGH, 2009].}$$

To calculate the 95 % confidence interval (CI) the logarithm of the odds ratio is needed. The formula below shows the calculation of upper and lower CI values. The term “ $z(1-0.05/2)$ ” is needed to integrate the level of the confidence interval because a 95% CI for the logarithm of the odds ratio is obtained as 1.96 standard errors on both sides of the estimation [BLAND and ALTMAN, 2000; MCNEIL, 1996; MCHUGH, 2009].

$$\text{Lower CI: } \ln(OR) - z(1-0.05/2) \times SE(\ln(OR))$$

$$\text{Upper CI: } \ln(OR) + z(1-0.05/2) \times SE(\ln(OR))$$

The odds ratio of “1” shows that there is no difference between two groups, and no relationship between exposure (to depression) and the health outcome (overweight, obesity or in general increased body mass index). Meaning that if the confidence interval includes “1” the odds or chance of the outcome measured (overweight or obese BMI range) does not differ between groups [BLAND and ALTMAN, 2000; MCHUGH, 2009].

Fisher’s exact test was used to detect statistical significant differences between depression groups (healthy, one depressive episode, more than one depressive episode) and categories of body mass index (underweight, normal, overweight, obese). To quickly calculate fisher’s exact p-value I used GraphPad Prism 5 for

Windows, a statistic program downloaded from www.graphpad.com [GRAPHPAD, 2012].

4.3 DNA Isolation and Genotyping

Before genotyping of the rs25531 and rs4680 polymorphisms, DNA extraction from EDTA blood samples was performed using the Magna Pure LC DNA Isolation Kit (Roche) for extractions made at the Department of Laboratory Medicine of the Medical University of Vienna, Austria, for samples 1 to 260. Samples 261 to 352 were isolated using DNeasy Blood and Tissue Kit (Quiagen) at the “Anna-Spiegel-Forschungsgebäude” at the medical-chemical and diagnostic laboratory of Univ. Doz .DDr. Harald Esterbauer.

4.3.1 Genotyping of rs25531

The 5' regulatory region of the SLC6A4 gene, which maps to 17q11.1-17q12, contains a 43 bp insertion/deletion polymorphism. Polymerase chain reaction (PCR) was performed with all of the 237 DNA samples using the primer pair 5'-TCCTCCGCTTTGGCGCCTCTTCC-3'/5'TGGGGGTTGCAGGGGAGATCCTG-3' to amplify long/short promoter (L/S) DNA fragments of the 5-HTTLPR polymorphism resulting in a 512 bp-long PCR product for the 16 repeat allele (long) and a 469 bp-long PCR product for the 14 repeat allele (short) [ANCHORDOQUY et al., 2003].

The PCR protocol which was used was adopted from *Wendland et al. 2006*, with only minor modifications. After an initial denaturation phase of 5 minutes at 95°C, 40 PCR cycles were used, consisting of a 45 second denaturation phase at 95°C, a 45 second annealing phase at 65.5°C and a 45 second elongation phase at 72°C. At the end of these cycles, a final 3 minute elongation phase at 72°C was added.

PCR reaction had a final volume of 25 μ L consisting of:

5x PCR MultiplexBuffer	5.0 μ L
MgCl ₂	2.5 μ L
dNTP Mix	1.5 μ L
TaqMan Hot Start Polymerase	0.2 μ L
ddH ₂ O	9.8 μ L
forward primer	2.5 μ L
reverse primer	2.5 μ L
DNA	1.0 μ L

[WENDLAND et al., 2006].

The PCR products were separated by gel-electrophoresis using 5% Criterion gels (Biorad) and dyed for 7 minutes with SYBR-green.

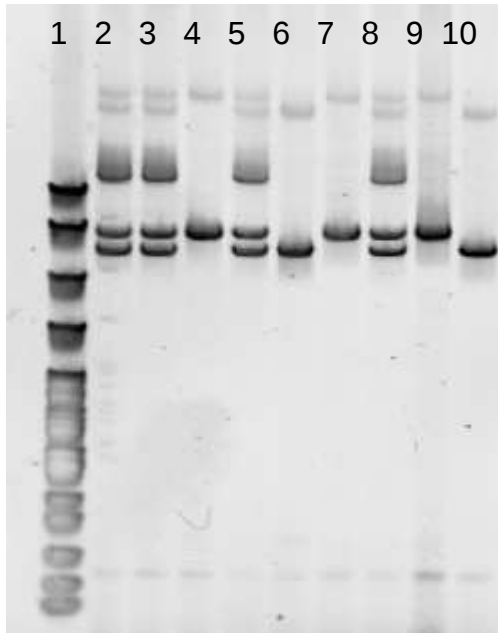


Figure 2. PCR products of the serotonin transporter length polymorphism. Slot 1 carries length marker to take readings of basepairs easily, slots 2, 3, 5 and 8 show heterozygous alleles (long and short), slots 4, 7 and 9 show the L-allele and slots 6 and 10 showing the S-allele.

Ongoing, the PCR reaction products were digested by HpaII (New England Biolabs) restriction enzyme for 8 hours – to ensure complete digestion – to detect rs25531.

Digestion products were separated on 2% agarose gels. *Table 3* shows the fragment length in base pairs at which alleles appeared.

Fragment length (bp)	Allele
469	S _A -allele
402 + 67	S _G -allele
512	L _A -allele
402 + 110	L _G -allele

Table 3. Fragment length of alleles after digestion.



Figure 3. Digestion products. Slot 1 carriers seize marker, Slots 2, 9, 10, 12 show S_A/L_G, Slots 3, 4, 6, 18, 21 show S_A/L_A, Slots 5, 11, 13, 14, 16, 20 show S_A/S_A, Slots 7, 8, 15, 19, 21 show L_A/L_A, Slot 17 shows S_A/S_G.

Figure 3. Digestion products with PCR products of the Serotonin transporter length polymorphism.

L_G carriers were analysed together with S/S carriers because of the lower SERT expression properties compared with L_A carriers [PARSEY et al., 2006; ANCHORDOQUY et al., 2003].

4.3.1 Genotyping of rs4680

According to Ruiz-Sanz et al., 2007, ARMS-PCR was performed to detect rs4680 Val158Met. Two primer pairs were used for detection of the different alleles: Primers 1 and 2 were used for the 626bp band, which served as internal control. Primers 3 and 4 were used to distinguish Val and Met allele. A specific base mismatch of primers 3 and 4 was used to create a hybridization bias for either of the two. The use of these specific primers results in a 451bp band for the Val allele and a 222bp band for the Met allele. Figure 4 shows the schematic primer design.

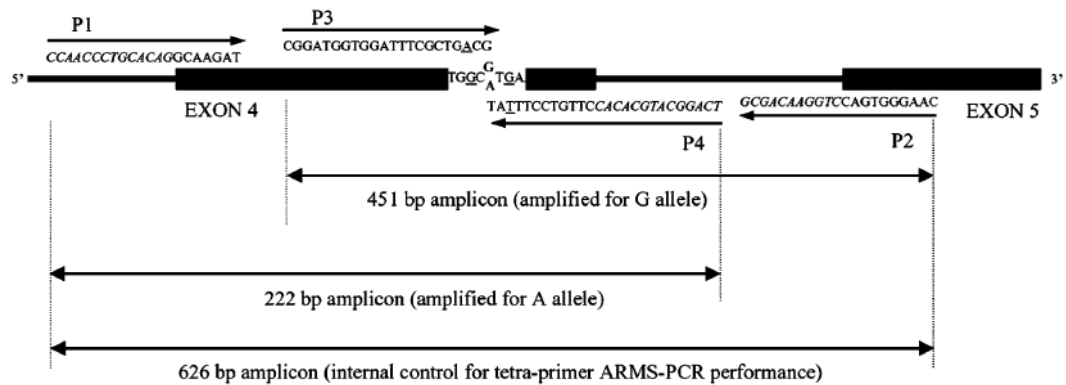


Figure 4. COMT primer design.

PCR reaction had a final volume of 24 μ L consisting of:

5xGreenBuffer	5 μ L
MgCl ₂	2.5 μ L
dNTPs (Mix)	1.75 μ L
TaqMan Hot Start Polymerase	0.2 μ L
ddH ₂ O	11.65 μ L
Primer1	0.45 μ L
Primer2	0.8 μ L
Primer3	0.45 μ L
Primer4	0.2 μ L
DNA	1 μ L

Amplification was made in a thermocycler with an initial denaturation at 94°C for 4 minutes, followed by 35 cycles of: 94°C for 30 s, 62°C for 30 s and 72°C for 20 s. Final extension was made at 72°C for 5 minutes. After the PCR all PCR products were separated by gel-electrophoresis using 5% Criterion gels (Biorad) and dyed for 7 minutes with SYBR-green. This visualises 3 bands in heterozygotes (626, 451 and 222 bp) and two bands in homozygotes (Met/Met shows bands at 626 and 222 bp, Val/Val shows bands at 626 and 451 bp) [RUIZ-SANZ et al., 2007].

Figure 5 shows the result of a successful PCR. Slots 1, 2, 12 show Val homozygotes, Slots 3, 7, 11 show Met homozygotes. Slots 4, 5, 6, 10, 12 and 13 show heterozygotes (Val158Met), Slot 8 carries size marker and 7 shows the control (no DNA added).

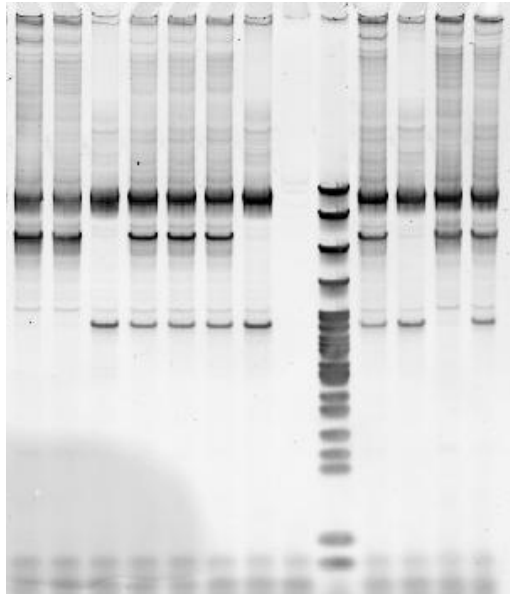


Figure 5. Successful PRC of the Serotonin transporter length polymorphism.

4.4 Measurements of personality traits

4.4.1 Five Factor Theory of Personality - NEO five factor inventory (NEO-FFI)

Costa and McCrae, 1992 suggested that personality traits can be summarized in terms of a five factor model. NEO is the acronym for the three main personality traits in the model – neuroticism, extraversion, openness. “The five factor inventory aims to help clinicians to understand the patient and to help formulating a diagnosis for better treatment for patients [COSTA PT and MCCRAE RR, 1992]”.

The following attributes are related to the five personality traits: “Good-naturedness, cooperativeness and trust are typically for *agreeableness*, whereas *neuroticism* is associated with emotional instability, resentment and being upset. *Openness* is related to originality, curiosity and ingenuity. *Extraversion* is characterized by talkativeness, assertiveness and energy and orderliness, responsibility and dependability are characteristics of *conscientiousness* [SJDM, 2012]”.

In the 1990ies, a Japanese study revealed the relationship between personality and body mass index and reported positive associations of extraversion with overweight in men and women while extraversion was inversely related to elevated body weight [KAKIZAKI et al., 2008]. Similar findings were reported by *Valenti et al., 2011* who suggest stronger proneness of severely obese bariatric surgery patients to impulsivity, irritability and instability [VALENTI et al., 2011].

A study from *Brummett et al., 2006* showed that neuroticism was significantly and positively related to body mass index in women only while extraversion was related to BMI in men only. Conscientiousness, openness and agreeableness were negatively related to BMI in both genders [BRUMMETT et al., 2006]. These gender differences in BMI related to personality were former described by *Faith et al., 2001* [FAITH et al., 2001]. These findings were confirmed by *Sutin et al. 2011* reporting the strongest association of elevated BMI with impulsivity. They found in a longitudinal study that high neuroticism, low conscientiousness and low agreeableness were related to higher body mass index and higher body weight variability during [SUTIN et al., 2011].

5 Results

5.1 Statistical Analysis

All statistical calculations were made by IBM SPSS 20.0, Graphpad Prism 5 or calculated by the equations listed in chapter 4, Methods.

5.2 Genotyping

Table 4 shows the number of males and females belonging to the different allele groups. There used to be more L_A homozygote males (32.1 %) compared to females (25.2 %) in the study population. Overall, 71.9 % were S_A , S_G , L_G carriers versus 28.1 % L_A homozygote. 78.2 % of the study population are carriers of the rs4680 Met allele while only 21.8 % are Val homozygotes. Being Val homozygote is more common in women with 25.9 % compared to 16.2 % in men in the study population.

SLC6A4 – rs25531	Male	Female
S_A , S_G , L_G	74	110
L_A homozygote	35	37
COMT – rs4680	Male	Female
Val homozygote	17	37
Met carrier	88	106

Table 4. Allele group distribution in both genes.

5.4 Statistical Analysis of Body Mass Index

The box plot shows BMI distribution over the three categories, defined for depression (healthy, one depressive episode and more than one depressive episode) data was split by gender. BMI seems to be decreasing depending on

number of depressive episodes in males, the relationship between BMI and number of depressive episodes seems to be inverse in females. A box plot was used because it shows variance and outliers. Most noticeable finding is probably that the variability of body weight is huge in females with more than one depressive episode, not only compared to men in the same group but also compared to females belonging to the other groups.

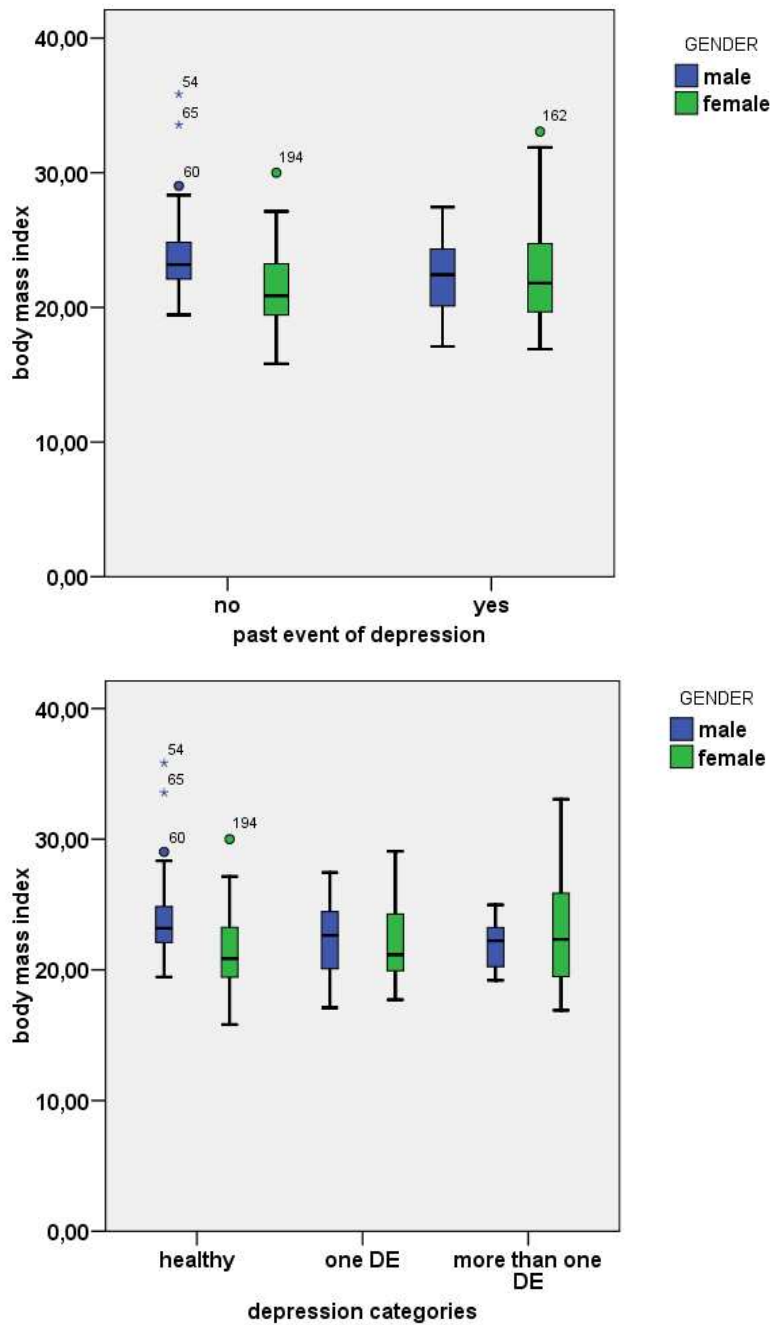


Figure 6. Box plot showing body mass index within health and depression as well as depression groups split by gender.

While variability in BMI seems to be highest in women with more than one depressive episode, it seems to be lowest in men with more than one depressive episode.

5.2.1 Testing of hypotheses

The hypothesis was that there is a significant difference in BMI between healthy participants and those with more than one depressive episode.

GENDER		BMI				Total
		>18,5	18,5-24,99	25-29,99	<30	
male	healthy	0	50	13	3	66
	one DE	2	18	3	0	23
	more than one DE	0	13	0	0	13
	Total	2	81	16	3	102
female	healthy	8	65	9	1	83
	one DE	1	23	6	0	30
	more than one DE	2	18	4	4	28
	Total	11	106	19	5	141

Table 5. Numbers of participants categorized into BMI and depression groups split by gender.

78.3 % of healthy female participants were within the healthy BMI range, only 9.6 % were underweight, 10.8 % were overweight and 1.2 % were obese.

14.3 % of women with more than one depressive episode had an increased BMI within the overweight category and 14.3 % were obese. 64.3 % of those were in the healthy BMI range indicating that depression is associated with an increase in body mass index.

75.8 % of healthy male participants were within the healthy BMI range, 19.7 % were overweight and 4.5 % were obese. No healthy participant is underweight.

The number of participants in the overweight category decreases with the number of depressive episodes in men. 13 % of men with one depressive episode were overweight whereas none of the males with more than one depressive episode was overweight or obese compared to 19.7 % overweight / 4.5 % obese participants within the lifetime healthy group.

This differential effect can be due to the small sample size. Another explanation for this inverse relationship would be that there is a gender-specific effect. Meaning that becoming overweight or obese after experiencing depression is only true for women. It has to be noted that BMI was calculated from self-reported weight and height data. Usually overweight and obesity are more common among the Austrian population with percentages of 52 for overweight and 13 for obesity in men and of 31 for overweight and of 9 for obesity in women (all aged from 18 to 65) [WHO, 2012d]. Meaning that BMI distribution of the study populations differs from the general population. This can be due to under-reporting weight and/or over-reporting height. *Glaesmer and Brähler 2002*, report that body mass index calculated from self-reported data tends to be not precise [GLAESMER and BRÄHLER, 2002]. After correction of body mass index according to *Gorber et al. 2008*, using the reduced model 4, prevalence of overweight increased to 16.3 % in women and 27.3 % in men and prevalence of obesity increased to 2.7 % in men and 5.4 % in women which would be more realistic regarding the general population. Another explanation for the small number of overweight and obese subjects could be that most of the lifetime healthy participants were students from the Medical University of Vienna who were more concerned about their weight compared to the general population.

In the next step, odds ratio and confidence intervals were calculated for women and men separately. *Table 6* shows the results for women:

	Odds Ratio (OR)	ln (OR)	Standard Error	95 % CI	Fisher's exact p value two-sided, $\alpha=0.05$
nDE=1 and overweight	1.8841	0.633	0.58	0.6 – 5.87	0.352
nDE>1 and overweight	1.6049	0.473	0.66	0.44 – 5.82	0.487
nDE>1 and obesity	14.44	2.67	1.15	1.52 – 137.41	0.013

Table 6. OR and 95% CI and Fisher's exact p-value calculation for women.

The odds-ratio, an item describing the strength on an association, shows that in the group of females with more than one depressive episode are 14 times more obese participants than in the lifetime healthy group without depression related symptoms. All of the other comparisons did not reach statistical significance.

In men, the relationship between body mass index and depression seems to be inversely. Unfortunately I couldn't test whether the odds of being underweight after having experienced depression in men because of lacking healthy participants being underweight. Therefore I tested whether the Odds Ratio of being overweight after one depressive episode is smaller compared to healthy participants.

Table 7 shows the results for men:

	Odds Ratio (OR)	ln (OR)	Standard Error	95 % CI	Fisher's exact p value two-sided, $\alpha=0.05$
nDE=1 overweight	0.641	-0.445	0.7	0.16 – 2.51	0.75

Table 7. OR and 95% CI and Fisher's exact p-value calculation for men.

Men in the group with one depressive episode are not as likely to become overweight as healthy participants. It must be noted that this effect did not reach statistical significance.

This indicates again a gender specific association of depressive events and increased body mass index, whereas women are at higher risk to become obese.

No male participant who experienced depression was obese and in the group of men with more than one depressive episode there was not even an overweight subject. A mean BMI of 21.79 (± 1.7 standard error) within males with more than one depressive episode indicates that although they have a normal BMI it lays within the lower healthy range.

Fisher's exact p-value does not reach statistical significance in any of the calculations except for females being more likely to become obese after having experience more than one depressive episode. Therefore the results above indicate that depression alone cannot explain variances in body mass index.

Next I wanted to test whether body mass index differs between the two allele groups of the serotonin transporter polymorphism rs25531. Figure 7 shows the distribution of the body mass index over the two allele categories:

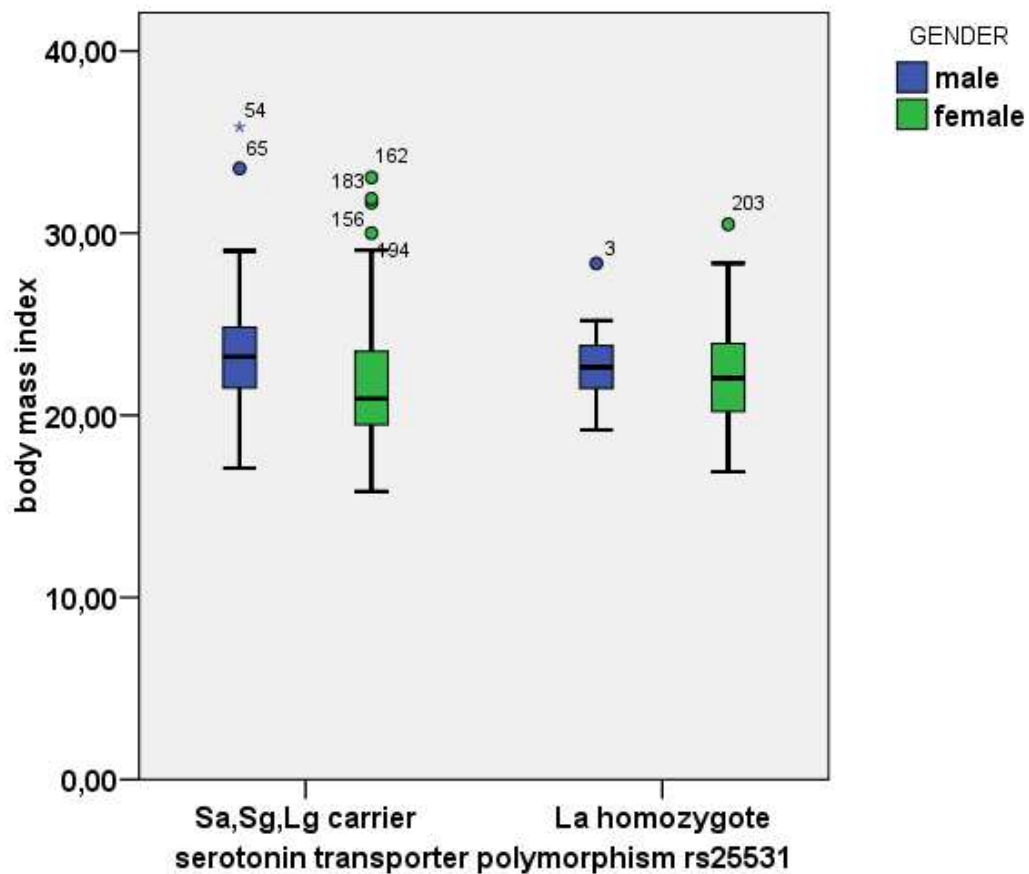


Figure 7. Box plot showing BMI scale for the different allele groups of the serotonin transporter polymorphism SLC6A4, split by gender.

L_A homozygote participants show less variability in body weight compared to S_A, S_G, L_G carriers. T-test revealed that there is no mean difference in body mass index between the two allele groups ($p=0.159$ for men, $p=0.502$ for women, respectively).

The same procedure was used to analyse differences between the alleles of the COMT rs4680 polymorphism. Met carriers were compared with Val homozygotes because of the Met related to decrease COMT enzyme activity. Figure 8 shows the distribution of the body mass index over the two allele categories:

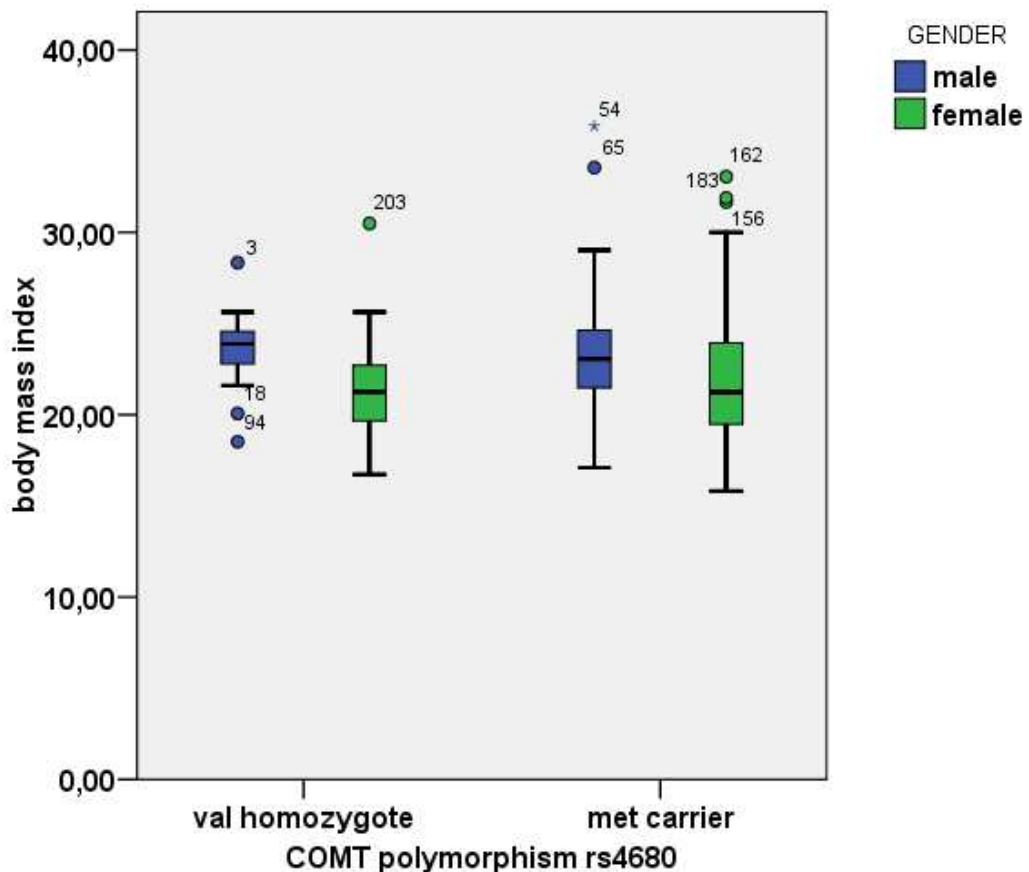


Figure 8. Box plot showing BMI scale for the different allele groups of the COMT polymorphism, split by gender.

Again, the picture shows that Val homozygotes seem to have less variability in BMI compared to Met allele carriers, similar to the rs25531 polymorphism of the serotonin transporter gene. T-test revealed that there is no mean difference in body mass index between the two allele groups ($p=0.601$ for men, $p=0.238$ for women, respectively).

Although there seems to be a trend that mean body mass index is higher in S_A , S_G , L_G allele carriers and Met allele carriers this could not be confirmed by statistical analysis.

As mentioned before, depression alone can only explain a little part of the differences in body weight (no significant difference in BMI between the three depression related groups, ANOVA: $p=0.537$).

Therefore I analysed the sample by using ANCOVA (Analysis of Covariance). Normal distribution of the dependent variable 'body mass index' was given.

Gender, age, age of depression onset and LEQ (a questionnaire for life events that have occurred in the past) as well as COMT and SLC6A4 genotypes served as covariates. To reduce the number of covariates I did a factor analysis first. This reduces the dimension of all the factors and leads to only one factor that needs to be included into the ANCOVA which makes the analysis even clearer.

Controlling for these depression- related factors led me to the following outcome:

The question was "does the mean body mass index differ between subjects having experience depression compared to those lifetime healthy after controlling for depression related factors like LEQ, COMT and SLC6A4 genotype as well as age and gender"? Unfortunately, the answer is no. The number of depressive events (healthy, one depressive episode or more than one) could not explain the differences in BMI after controlling for the above mentioned factors ($p=0.694$, $\alpha=0.05$).

Another analysis was calculated including the factors COMT, LEQ, and number of depressive events. This analysis was done for women only because the important cofactors and covariates might differ between males and females.

The question was 'does mean BMI differ between the three depression groups (healthy, nDE=1, nDE>1) after controlling for COMT, LEQ and number of depressive events'. Only the number of depressive events had a significant impact in the model ($p=0.05$) and overall the model became significant and could account for 10% of the difference in mean body mass index.

The same analysis was calculated for men with only changing COMT to SLC6A4 polymorphism. Although none of the included cofactors and covariates had a significant impact within the model (not even the interaction term) the fixed factor depression categories (healthy, nDE=1, nDE>1) became significant ($p=0.03$) and could explain 6.9 % of the variance in body mass index.

Considering that all of the subjects were healthy when they were recruited for the study, meaning that those having experienced depression before have been remitted at the time of inclusion. This led to the question whether not the fact of having experienced depression in the past, but certain personality traits (evaluated with different personality scales) might be able to explain differences in mean BMI.

To test whether mean NEO-FFI scores differ between BMI categories I used a non-parametric Kruskal-Wallis test. Table 8 shows the SPSS output of each dimension of the NEO five factor inventory personality trait scale, indicating that mean agreeableness and mean openness differs between the four BMI (underweight, normal, overweight, obese) groups.

Statistics (a,b)					
	NEUROTICISM	EXTRA- VERSION	OPENNESS	AGREE- ABLENESS	CONSCIENT- IOUSNESS
Chi- Quadrat	2,986	5,761	8,369	8,026	1,177
df	3	3	3	3	3
Asympt. sign.	,394	,124	,039	,045	,759
a Kruskal-Wallis-test b group variable: BMI_CATEGORIES					

Table 8. Mean differences of personality trait scores of the four BMI groups.

Analysis of covariance (ANCOVA) revealed that 23.6 % of the difference in mean body mass index can be explained by agreeableness. After controlling for the depression-related factor (dimension reduced factor consisting of gender, age, number of depressive episodes, COMT and SLC6A4 genotype and LEQ), 27 % of the difference in mean body mass index could be explained by agreeableness.

All of the other traits of the NEO FFI like neuroticism, extraversion, openness and conscientiousness failed to reach statistical significance.

Table 9 shows the SPSS output for hypothesis that differences in the mean body mass index are related to agreeableness:

Tests of Between-Subjects Effects						
Dependent Variable: BMI_SR						
Source	Type III Sum of Squares	df	Mean Square	F	Sig.	Partial Eta Squared
Corrected Model	624,516 ^a	37	16,879	2,020	,001	,270
Intercept	44831,264	1	44831,264	5366,118	,000	,964
DE_related factor	,756	1	,756	,090	,764	,000
AGREE	624,312	36	17,342	2,076	,001	,270
Error	1687,610	202	8,355			
Total	124358,979	240				
Corrected Total	2312,126	239				
a. R Squared = ,270 (Adjusted R Squared = ,136)						
Table 9. SPSS output for hypothesis that differences in the mean body mass index are related to agreeableness.						

Testing lifetime healthy and remitted patients separately revealed that 45.6 % of the variance in BMI in healthy males is related to extraversion (ANCOVA, $p=0.03$). All of the other personality traits did not reach statistical significance in this context neither in males nor in females.

Non-parametric correlation (Spearman correlation) showed that self-reported BMI and agreeableness correlate inversely in men (correlation coefficient -0.347; $p=0.003$) but not in women.

Impulsivity, neuroticism and extraversion, personality traits that have been associated with BMI in other studies could not be shown to correlate with BMI in this analysis. This might be due to different personality trait scores due to history of depression and characteristics of the study population. Interestingly

impulsivity (BIS-10 scale) did not correlate with BMI although it has former been described as a predictor for weight change and body weight variability [VALENTI et al., 2011]. Irritability, one of the characteristics of neuroticism, on the other hand correlated well with self-reported BMI (correlation coefficient 0.202, $p=0.011$) in the healthy but not in the remitted population.

It has to be noted that all analyses were done with body mass index from self-reported data. Changing the dependent variable from self-reported body mass index to corrected body mass index (corrected body mass index according to *Gorber et al., 2008*) slightly changed the results but made none of them statistically significant.

5 Discussion

Although most results did not reach statistical significance they point out that becoming overweight after experiencing depression is more common in women whereas men are more likely to become underweight or stay within the normal weight range.

Sookoian et al., 2007 showed that reduced serotonin transporter activity, genetically determined by being S homozygote or carrying the L_G allele of the serotonin transporter polymorphism rs25531, is associated with higher BMI and with greater variability in body weight compared to L_A homozygote participants [SOOKOIAN et al, 2007]. Although the boxplots shown in the results section point in the same direction, no significant difference between the two allele groups could be found. L_G and S allele carriers are more likely to become depressed under certain environmental conditions and their amygdale activity is altered compared to L_A homozygotes which might lead to increased emotionality resulting in overeating whereas L_A homozygotes are more likely to have a stable personality and are less irritable. This might prevent them from emotionalising food and from overeating when certain stressors occur. It might be the case that the study population, consisting mainly of students from the medical university in Vienna, is not eligible for this special analysis due to the fact that their health consciousness, lifestyle and eating behaviour might be different than that of the general population. Another reason why differences might not have been detected is that the sample size was relatively small. Analysis was made with overall 258 participants wherefrom 141 were healthy, compared to *Sookoian et al, 2007* who analysed 934 healthy students [SOOKOIAN et al, 2007].

Similarly to rs25531, Met allele carriers of the COMT rs4680 polymorphism show greater variability in body mass index. This might be due to lower synaptic dopamine levels in reward related brain areas in Met carriers resulting in overeating to compensate for this deficiency [STICE et al., 2011]. Wang et al., 2007 reported involvement of COMT polymorphisms in obesity and highlighted

the importance of estrogen metabolism in this context although they could not show a significant correlation between the polymorphism and body mass index. Although being Met allele carrier seems to point at increased susceptibility for having an elevated body mass index, this could not be confirmed. Of note is that although the test did not get statistically significant neither in women nor in men, p-values between genders differed enormously (men: $p=0.601$; women: $p=0.238$). One attempt to explain this outcome would be the difference in male and female participants another one would support the involvement of COMT in the estrogen metabolism.

Regarding analysis of personality traits, inverse associations between body mass index and agreeableness could be found which is in accordance with Brummet et al., 2006 who showed that agreeableness was negatively correlated with BMI in both genders.

Only few findings of former studies that have been conducted in the past could be confirmed in this analysis. This might be due to the fact that remitted participants, although they were healthy at the time screening, differ from lifetime healthy participants regarding personality trait scores.

6 Conclusion

The analysis revealed that women are more likely to become obese after more than one depressive episode whereas men do not even become statistically significantly more overweight compared to lifetime healthy men. One explanation for this finding could be that experiencing depression results in overeating in women whereas men are more prone to illicit drug abuse, tobacco smoking and alcohol consumption.

Personality plays a role in becoming overweight, obese – agreeableness negatively associated with BMI. Irritability associated with BMI in healthy but not in remitted. Irritability has former been described as a risk factor for binge eating and variability in body weight over time. Regarding the remitted population this picture might have been different if they were experiencing a depressive episode at the time screening.

Limitations:

The reported BMI does not reflect general Austrian population which might be due to recruiting method. Students of the Medical University of Vienna, mainly, who might be more active and more prone to a healthy lifestyle due to their education. Self-reported height and weight might leads to underestimation of BMI (men overestimate height, women underestimate weight).

Another limitation would be that the sample is too small. Effects of the two polymorphisms might not be detected because of the small sample size.

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Abstract

Overweight and obesity are major public health concerns and although the disease is preventable the number of obese or overweight people is still rising. Depression ranks among the leading causes of disability and reduced life quality. The high prevalence and heritability of both diseases as well as their shared comorbidities and in part shared pathophysiology makes it highly interesting to analyse them together. In this master thesis I wanted to analyse two depression related genes and their effect on body weight, mood and personality traits. Blood samples were collected from all participants to analyse two common polymorphisms (serotonin transporter polymorphism rs25531, COMT polymorphism rs4680), body mass index was calculated from self reported height and weight. Questionnaires were given to the participants to collect data about their personality traits. Analysis of covariance was calculated to reveal the effect of depression and depression related genes on body mass index. Unfortunately, no clear direction of causality could be shown. Although the number of depressive events seems to play a role in the context of overweight and obesity neither rs25531 nor rs4680 could be shown to have a significant effect. Regarding personality traits, only one clear conclusion could be drawn namely that agreeableness is negatively associated with BMI. Larger, longitudinal studies would be needed to show clearer results.

Zusammenfassung

Übergewicht und Adipositas gehören zu den größten Gesundheitsproblemen dieser Zeit. Trotz der Möglichkeit der Prävention und gegenwärtigen Durchführung von Präventionsmaßnahmen durch Medien und in Schulen steigt die Zahl der übergewichtigen bzw. adipösen immer weiter an. Depression ist eine weitere Krankheit die durch ihre hohe Prävalenz und ihr hohes Maß an Erbllichkeit weiter in den Fokus der Öffentlichkeit, aber auch der Forschung rückt. Übergewicht/Adipositas und Depression bringen zumindest teilweise die selben Komorbiditäten mit sich. Eine teils gemeinsame Pathophysiologie der Krankheit kann nicht ausgeschlossen werden. Studien konnte aber bisher nicht belegen ob Depression zwangsläufig zu Übergewicht führt bzw. dass Übergewicht zu Depression führt. Beide Wege sind möglich und müssen in Betracht gezogen werden.

Ziel dieser Arbeit war herauszufinden ob Studienteilnehmer mit einer vorhergehenden Depression eher übergewichtig oder sind als jene, die nie unter Depression litten. Weiters sollten zwei aus der Depressionsforschung bekannte Polymorphismen (rs25531 und rs4680) in die Analyse miteinbezogen werden und ihr Stellenwert in diesem Kontext sollte ermittelt werden. Blutproben wurden von allen Probanden, zur Gewinnung von DNA Proben und damit zur Identifizierung der Allele-Verteilung innerhalb der Studienpopulation, gewonnen. Der Body Mass Index wurde aus den Größen- und Gewichtsangaben der Probanden errechnet. Leider konnte kein signifikanter Effekt der beiden Polymorphismen auf den BMI festgestellt werden.

Fragebögen zur Erhebung von Persönlichkeitsmerkmalen wurden von den Studienteilnehmern ausgefüllt. Daraus konnten weitere Analysen erfolgen die sich mit Körpergewicht und Persönlichkeit befassten. Es ergab sich, dass der BMI negativ mit „Agreeableness“, einem der Persönlichkeitsmerkmale des NEO-FFI, korrelierte. Je höher als die „Verträglichkeit“ desto niedriger war der Body Mass Index.

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Education

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02/2011-06/2012	General Hospital Vienna, Neuroimaging Working Group of Assoc.Prof. Priv.Do. Dr. Lukas Pezawas ▪ managing and implementing genetic analysis in depression related studies
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