Genetic Overlap Between Obsessive-compulsive Disorder and Major Depression

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GENETSKO PREKLAPANJE OPSESIVNO-KOMPULZIVNOG POREMEĆAJA I DEPRESIJE

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SUMMARY

Obsessive-compulsive disorder and major depressive disorder are among the most common mental disorders globally and are frequently co-diagnosed. They are both highly complex, heterogenous and a result of both environmental and genetic factors. This review focuses on the genetics behind these disorders and their overlap. When researching OCD, the genes that have most commonly been associated with the disorder are ones involved in glutamate, serotonin, and dopamine transmission. Such genes include *SLC1A1*, *DLGAP3* and *DRD4*. In MDD genetics, genes related to neurotransmission, like *TPH2*, are also relevant but so are genes involved in several other biological pathways, like *BDNF, LHPP, SIRT1* and *NEGR1* which are involved in mitochondrial biogenesis, cell adhesion or neuronal survival. When researching the overlap between OCD and MDD, common mechanisms, shared genes and treatment effects must all be taken into consideration. Besides irregularities in neurotransmission, reduced amygdala and hippocampal volumes have also been observed in both OCD and MDD patients, as well as abnormalities in the regulation of the HPA axis. That implies shared genes between the two disorders may be involved in those mechanisms. 5-HTTLRP, a functional polymorphism of the *SLC6A4* gene has most consistently been associated with both disorders and it affects the serotonin transport. Another gene relevant to both OCD and MDD involved in the same pathway is *HTR2A*, while *FKBP5* is a gene affecting HPA axis regulation and shows great promise in researching the overlap of these disorders. The shared treatment effects, such as SSRIs and neuromodulation therapy, further confirm the idea of shared genes. These and future findings about the genetic overlap between OCD and MDD will help develop better and more effective treatment for people suffering from both these disorders.

Key words: OCD; MDD; genetic overlap; review

SAŽETAK

Opsesivno-kompulzivni poremećaj i depresivni poremećaj među najčešćim su mentalnim poremećajima na globalnioj razini, te su često zajedno dijagnosticirani. Oboje su vrlo kompleksni, heterogeni poremećaji koji nastaju kao rezultat okolišnih i genetičkih faktora. Ovaj se rad fokusira na genetiku oba ova poremećaja i njihovo preklapanje. Pri istraživanju OKP-a, geni najčešće povezivani s ovim poremećajem su oni vezani uz prijenos glutamata, serotonina i dopamina. Neki od tih gena su SLC1A1, DLGAP3 I DRD4. U genetici depresivnog poremećaja, izuzev gena vezanih za neurotransmisiju, poput TPH2, također su relevantni i geni vezani za druge biološke puteve poput mitohondrijalne biogeneze, adhezije stanica i neuronalnog preživljavanja. Neki od tih gena su BDNF, LHPP, SIRT1 i NEGR1. Prilikom istraživanja preklapanja ova dva poremećaja, zajednički mehanizmi, geni i efekti liječenja moraju biti uzeti u obzir kako bi dobili što bolju predodžbu. Izuzev nepravilnosti u neurotransmisiji, smanjen volumen amigdale i hipokampusa uočen je kod pacijenata oboljelih od oba poremećaja, kao i abnormalnosti u regulaciji HPA osi. To ukazuje kako je vjerojatno da će zajednički geni biti oni vezani za te mehanizme. 5-HTTLPR, funkcionalni polimorfizam SLC6A4 gena koji djeluje na transport serotonina najčešće je povezivan s oba poremećaja. HTR2A je također gen koji djeluje na isti mehanizam, dok je FKBP5 gen povezan s regulacijom HPA osi te se smatra vrlo obećavajućim za buduća istraživanja. Slični pristupi liječenju, poput SIPPS-a i neuromodulacije, dodatno potvrđuju ideju o postojanju zajedničkih gena između OKP-a i depresivnog poremećaja. Ova I buduća saznanja o genetskom preklapanju ova dva poremećaja pomoći će razvitku novih i učinkovitijih lijekova za osobe koje boluju od OKP-a i depresivnog poremećaja.

Ključne riječi: OKP, depresivni poremećaj, genetsko preklapanje

CONTENTS

1. Introduction

1.1. Obsessive-compulsive disorder

Obsessive-compulsive disorder (OCD) is a mental illness that belongs to the obsessive-compulsive and related disorders (OCRDs). OCRD are a set of mental conditions characterised by intrusive and unwanted thoughts and preoccupations along with related repetitive behaviours. According to the 11th Revision of International Classification of Diseases (ICD-11) this group also includes Tourette syndrome, hoarding disorder, excoriation, body dysmorphic disorder, trichotillomania, olfactory reference syndrome and hypochondriasis, but OCD is considered the key example (1).

The main characteristic of OCD is the presence of obsessions and/or compulsions. Obsessions are defined as unwanted and intrusive thoughts, impulses, urges and images which are repetitive and persistent. On the other hand, compulsion is a term used to describe repetitive mental acts or behaviours that an individual performs driven by the need to achieve a sense of completeness. The urges to complete such tasks stem from obsession-driven rigid rules that a person feels forced to follow in order to achieve a feeling of calmness and satisfaction. Since most of the patients are highly aware of their symptoms and wish they could control them better, another common characteristic of OCD is the avoidance of a range of activities by patients in order to avoid being triggered or experiencing obsessions (2).

There is a commonly used model used to describe OCD symptoms. It is a four or five-factor model that categorises common sets of obsessions and compulsions into dimensions, such as those about contamination and cleaning, intrusive aggressive or sexual thoughts and concerns about symmetry (Table 1). In addition to these, in rare cases OCD can manifest with different, less common, symptoms such as musical obsessions or scrupulosity.

These dimensions have been observed in patients all around the world suggesting that OCD is a homogenous disorder. It is amongst the most common mental disorders globally with a lifetime prevalence of 2-3%. In both sexes the onset of OCD typically happens early in life, between the ages of 18 and 29, but it is more common in females in which the onset usually happens during adolescence or less common in peripartum or postpartum periods. Additionally, it is found across all socioeconomic classes and in countries with varying income, although cultural and social factors impact the experience and expression of OCD symptoms (focusing on different sources of contamination among others) (3).

Dimension	Obsessions	Compulsions
1. Contamination	Concerns about sources of contamination such as germs	Cleaning, showering
2. Harmful thoughts	Concerns about being harmed themselves or other people being harmed	Checking
3. Forbidden thoughts	Intrusive religious aggressive, or sexual thoughts	Praying, mental rituals
4. Symmetry factor	Concerns about symmetry	Counting, repeating, straightening, ordering
5. Hoarding factor	Hoarding, saving	Hoarding behaviours

Table 1. **Dimensions of OCD symptoms. Information from** (3)

1.2. Major depressive disorder

According to the Diagnostic and Statistical Manual of Mental Disorders 5th edition, major depressive disorder (MDD) is a mental disorder characterised by at least one depressive episode lasting no less than two weeks (2). A

depressive episode is defined by having at least 5 symptoms linked to changes in moods and interests, sleeping and eating patterns and impaired cognitive functions. Some of those symptoms are depressed mood, fatigue and loss of energy, feelings of worthlessness and/or inappropriate guilt, insomnia or hypersomnia, diminished interest or pleasure in almost all activities and considerable weight loss or gain due to changes in appetite. In order to diagnose MDD these symptoms must interfere with the patient's everyday life and the episode must not be attributable to the effects of substance abuse or other medical conditions. There are several specifiers of MDD that help determine clinical subtypes of the conditions. These include severity, and the presence of anxious distress, mixed features, melancholic features, psychotic features with peripartum onset or a seasonal pattern.

MDD is a disease which variates considerably in remission and symptom severity from patient to patient. Higher psychiatric comorbidity and symptom severity, along with childhood trauma corelate with less favourable course of the disease and higher chances of MDD recurrence. Even after treatment and recovery residual symptoms and different functional impairments are still present in most patients.

MDD is almost two times more common in females than in males and episodes in women tend to last longer and occur more frequently. The median age of onset of MDD in both sexes is 25 years, and the peak risk period is from mid-to-late adolescence through to early 40s. Although it may sometimes be heard that MDD is a "disease of the modern world", it has actually been shown that the 12-month prevalence of MDD is very similar in high and low-income countries. Additionally, the symptoms, age of onset, severity and other socio-demographic and environmental factors are mostly comparable between different countries and cultures, with the biggest disproportion in available resources for patient care and the quality and availability of treatments (4).

1.3. Purpose of the review

Major depression disorder and obsessive-compulsive disorder are both highly prevalent mental disorders on a global level, and both cause diminished quality of life and functional impairment of the patients suffering from them. OCD has a 12-month prevalence rate of 0.7–1% and a lifetime prevalence rate of 2-3% (5). MDD is one of the most common illnesses worldwide, with a 12-month prevalence rate around 6% and a lifetime prevalence three times higher, which indicates that one out of every 6 people suffers from MDD at least once in their lifetime (4). About 65-85% of OCD patients suffer from another mental disorder during their life, usually another OCRD, but sometimes these can be anxiety and mood disorders or substance use disorders.

The most common diagnosis to co-occur along with OCD is MDD, which is present in 15-39.5% of OCD cases (6). In recent years genetic studies have shown that OCD shares a part of its genetic background with the disorders it co-occurs with, and the genetic corelation of OCD with MDD is estimated at 0.21 (6). Further studies of the genetic backgrounds of these disorders and their overlapping could help develop more efficient treatments in the future, especially for patients suffering from multiple diagnosis, as it will enable a more personalised and specific approach for each patient.

In the light of this, in this review I will attempt to highlight the most important findings in the genetics of both OCD and MDD, and also to summarise the similarities between their genetic backgrounds, in order to understand why these disorders are so often co-diagnosed and how big of a role genetics plays in it.

2. Genetics of OCD

OCD is a genetically heterogenous disorder with many underlying biological pathways. It is considered to be a result of various genetic and environmental factors, and is both familiar and heritable (7). The genetic architecture of the disorder contains a larger number of genes with modest impact, which cumulatively contribute to the risk of developing the disorder (8).

2.1. Hereditability

Family and twin studies are most commonly used for exploring hereditability and genetic contribution to OCD. Twin studies typically estimate the hereditability for OCD symptoms to be between 45 to 65% (9), while in a more recent twin study of obsessive-compulsive traits the hereditability was estimated at around 74%. The same study explored shared genetic factors among the dimensions of OCD symptoms and found that each dimension was heritable and shared genetics were accountable for their shared variance (10). A family and twin study done in 2013 found that the risk of developing OCD among relatives of OCD patients increases with the degree of relatedness to the patient, and is overall higher among relatives than in the general population (11). Results like this highlight the importance of exploring genetics of OCD in hopes of developing new and better treatment for the disorder.

2.2. Genes associated with OCD

Early studies of the genetics of OCD were mostly candidate gene studies. These are based on the already available information about the disorder. Genes of interest are chosen according to physiological and functional aspects

of the studied condition or based on the results of linkage studies done on families with the disease, and their variations are then analysed in connection with the observed phenotype (12). When studying OCD, the most common genes of interest are ones related to the serotonergic, glutamatergic and dopaminergic systems, because these biological pathways are known to be connected to the physiology of the disorder (13). The drawbacks of these studies are often insufficient prior knowledge on the disorder and mostly inconsistent findings when applied to all populations. Consequently, most of the research done today is based on different types of studies such as copy number variants studies, genome wide association studies (GWAS), whole exome sequencing, and gene expression analysis. Nevertheless, genes connected to glutamate, serotonin and dopamine neurotransmission remain relevant and are among the most commonly studied (12).

One gene that has often been researched is the Solute Carrier Family 1 Member 1 (*SLC1A1*) gene, which codes for the postsynaptic glutamate transporter protein EAAT3 (also known as EAAT1) (14)(15)(16). It was first suggested as a gene important for OCD by two GWAS, which identified an association peak in the 9p24 region of chromosome 9, the same region that contains the *SLC1A1* gene (17)(18). Since then, different approaches confirmed its significance. A study done on transgenic mice found that overexpression of the EAAT3 protein resulted in an anxiety-like phenotype and repetitive behaviour, and also that such behaviours were reversable when treated with fluoxetine and clomipramine, both antidepressants (19). That may open new possibilities in OCD treatment research. A family-based association study identified *SLC1A1* variants associated with OCD, and found that 7 out of 11 analysed SNPs were significantly connected with OCD. Some were associated with OCD in families in the total sample, while others were associated only with males or females in these families. (16).

Another gene connected to the glutamatergic system that is studied in relation to OCD is the DLG Associated Protein 3 (*DLGAP3)* gene, also known as *SAPAP3*. This gene encodes a postsynaptic scaffolding protein involved in glutamate transport. A study of *DLGAP3*-mutant mice showed that animals with deletion of this gene exhibited OCD-like behaviour, including increased anxiety and compulsive grooming. Defects in cortico-striatal synapses were observed in these mutant mice, which implies that these synapses might play a role in the physiology of OCD (20). A GWAS study from 2013 has shown that *DLGAP1*, a gene from the same family, might be relevant to OCD (21) and a more recent CNV study found that a duplication of an exon on this gene might contribute to the development of OCD (22).

DRD4 is also a promising candidate gene for understanding OCD. It encodes the dopamine D4 receptor and contains a variable number of tandem repeats sequence (VNTR). This polymorphism has previously been linked to OCD and it has been detected that it contains alleles with 2-11 repeats. An association analysis from 2012 showed that the frequency of the 7 repeats (7R) allele from that sequence is much greater in OCD patients, while higher frequency of the 2R allele was linked to symmetry dimension (23). A possibly relevant frameshift deletion of this gene was also discovered by genome sequencing as a part of an CNV study (22). Future studies are still needed to further research this gene and its significance.

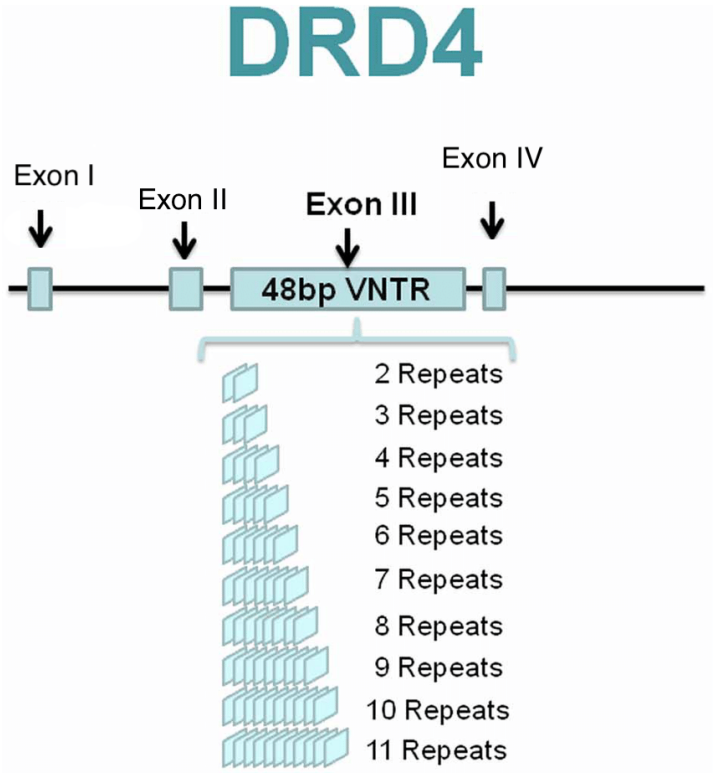

Figure 1**. Illustration of VNTR sequence on DRD4 gene with its multiple repeat alleles. Adapted from Smith et al 2020** (24)

A gene encoding oligodendrocyte lineage transcription factor 2, *OLIG2*, is highly expressed in brain areas linked to OCD (25). Because of this, *OLIG2* has also been studied in the context of OCD, and a family-based association candidate gene study has found that three SNPs of this gene are associated with the disorder (26). Another study analysed the three SNPs of *OLIG2* and found that they might be connected to different OCD dimensions, however studies with larger samples are needed to confirm this (27).

The genes described are some of the most commonly studied, but there are many more that have yet to be further explored. Some of the other genes that have been linked to OCD through different studies include *BTBD3*, *PTPRD*, *GRIK2* and *CDH10* (28)(29)(22).

Gene	Polymorphism associated with OCD	Encodes for	Role
SLC1A1	rs4740788, rs301443, rs4740788-rs10491734-rs10491733	postsynaptic glutamate transporter protein EAAT3	Glutamate transport
DLGAP3 **and** ***DLGAP1***	rs3866988 (*DLGAP1*)	postsynaptic scaffolding protein	Glutamate transport
DRD4	2R and 7R alleles on the VNTR sequence, a 13 bp frameshift deletion	dopamine D4 receptor	Dopamine transport
OLIG2	rs762178, rs1059004, rs9653711	oligodendrocyte lineage transcription factor 2	Motor neuron and oligodendrocyte differentiation

Table 2. **Summary of major genes associated with OCD**

3. Genetics of MDD

Like OCD, MDD is also considered a heterogenous disorder, manifesting with many different symptoms and varying in severity. It is considered to be a result of both genetic and environmental factors, which cumulatively increase the risk of developing MDD. Such environmental risks include various stressful life events such as marital issues, serious illness, or financial problems in one's personal life or social circle (28). They also include alcohol misuse, smoking and social deprivation (30). The genetic background of this disorder is considered to be polygenic, made up rare, high impact mutations and low impact gene mutations whose combined effect has a big impact on the possibility of experiencing symptoms of MDD.

3.1. Hereditability of MDD

The importance of genetic factors in developing MDD has been confirmed through twin and family studies, defining MDD as a hereditable and familial disorder. Twin studies have estimated the hereditability of MDD to be around 37% (31), while a family study in Scotland found that the heritability for recurrent MDD is higher than for single episode MDD. Family studies suggest that the risk of developing MDD among first degree relatives is two to three times higher than in controls (31). Establishing that genetics play an important role in the onset of MDD further support the need for studying and searching for relevant genes and variants in hope of broadening our knowledge on this disorder.

3.2. Genes associated with MDD

TPH2, a gene encoding a member of the tryptophane hydroxylase family, an enzyme in brain serotonin synthesis, has been researched in association with MDD. It is located on a region on chromosome 12, which was previously linked to borderline personality disorder, so its connection to mental disorders was already known. Many studies have confirmed the link between this gene and psychiatric disorders, including bipolar disorder and MDD (32). A study from 2005 identified a SNP in this gene that results in an ~80% decrease in the enzymes activity. Further analysis then found that the same SNP was present in 9 out of 87 patients with MDD in contrast to only 3 carriers among 219 controls. This confirmed that *TPH2* might be an important risk factor for the disorder (33). Along with *TPH2*, another gene involved in tryptophane catabolites pathways was also connected to MDD. SNPs on the *TPH1* gene have also been confirmed to correlate with the risk of developing MDD (34). Since SNPs on both these genes have been proven to impact the occurrence of MDD, it strongly indicates that the tryptophane catabolites pathway is involved in the development of this disorder.

Brain-derived neurotrophic factor encoding gene (*BDNF*) has been suggested as a possible gene of relevance when it comes to exploring MDD genetics, as it was shown that lower levels of this factor are present in blood samples of MDD patients (35). Although a study from 2005 failed to detect a connection between this gene and the disorder (36), another study from the same year has suggested that *BDNF* locus *Val66Met* might be relevant in haplotypic association to MDD (37). These inconsistent findings indicate that further research of *BDNF* might connect this gene to susceptibility to MDD.

A GWAS study done in 2015 identified two new loci that show great promise for progress in MDD genetics research. The study was done on 6000 Chinese women suffering from MDD and 6000 controls. The first significant

locus is the *sirtuin1* (*SIRT1*) gene on chromosome 10, which plays a role in mitochondrial biogenesis. This gene appears to be of even greater significance in melancholia, a subtype of MDD. When searching for genetic association with this subtype, signal at this locus has significantly increased. The other loci this study saw to be associated with MDD was an intron of the phosphorlysine phosphohistidine inorganic pyrophosphate phosphatase (*LHPP*) gene, also located on chromosome 10. The significance of both these loci has been confirmed in a replicated association study done on a separate cohort including both sexes where they have again been linked to MDD (38).

Although no specific genes have yet been discovered, when researching reoccurring, early-onset MDD, chromosome 15q has been linked to this subtype of the disorder. A linkage study from 2004 found significant linkage of this chromosomal region in relation to his type of MDD (39). A study done a few years later narrowed this region to 15q25-15q26 by linkage analysis. This study also did not find any specific genes responsible, but it demonstrated that this region increases susceptibility to MDD development (40). These results indicate that this region linked to MDD possibly consists of one or more genes whose variations have a significant impact on the development of reoccurring, early-onset MDD.

The neuronal growth regulator 1 encoding gene (*NEGR1*), which belongs to the immunoglobulin superfamily of cell adhesion molecules has also been researched in relation to MDD. A genome-wide significant SNP of this gene has been detected in two studies (41)(42), and the exact role of this protein in the biological pathways of MDD development is still being researched. A study done on *NEGR1*-deficient mice found that those animals, in contrast to controls, showed altered brain anatomy and hippocampal neuronal population along with behavioural differences. *NEGR1*-deficient mice exhibited MDD-like behaviour, such as a decline in social interactions and lack of whisker grooming which can be linked to inability to establish social hierarchy (43).

Another study has found that the *NEGR1* pathway is modulated by antidepressant treatment, meaning that it might be one of many biological mechanisms which influence the development of MDD (44). These types of studies with findings linking *NEGR1* to MDD will surely result in new and more specific information about this gene and its connection to this disorder.

In recent years additional genes have been linked to MDD, but have not yet been researched in significant detail. A GWAS study from 2018, the largest one so far, identified 44 loci connected to the disorder, including *CACNA1E, GRIK5* and *DRD2* (42). Future genetic studies will have to try to confirm the relevance of these genes and define the way they influence the development of MDD in order to have a wider knowledge on the underlying pathways that cause this disorder and how to cure or prevent it.

Gene	**Polymorphism associated with MDD**	**Encodes for**	**Role**
TPH2* and *TPH1	G1463A (*TPH2*) rs1799913, rs10488682, rs623580, rs18005832 (*TPH1*)	Isoforms of tryptophane hydroxylase	An enzyme in brain serotonin synthesis
BDNF	Val66Met	Brain-derived neurotrophic factor	Promoting neuronal survival in adult brain
SIRT1	rs187810158	Sirtuin1	Mitochondrial biogenesis
LHPP	rs145655839	Phosphorlysine phosphohistidine inorganic pyrophosphate phosphatase	Metabolism of nucleotides
NEGR1	rs1432639	Neuronal growth regulator 1	Cell adhesion

Table 3. **Summary of genes associated with MDD**

4. Genetic overlap between OCD and MDD

Since both OCD and MDD are familial and hereditable complex mental disorders that are very often co-diagnosed, the question can be raised as to why is that the case. When talking about these disorders it is most likely that the similarities rest on shared mechanisms in the brain, which are a result of shared genetic factors and result in similar treatment effects (45). That is why it is important to take into consideration similarities at all of these levels when researching the overlap between OCD and MDD. In this way, we can get the most complete idea about the complex shared background of these two disorders.

4.1. Shared brain mechanism

The amygdala is a structure located in the medial temporal lobe of the brain and that plays an important role in mediating emotional responses, especially fear conditioning. Neuroimaging studies found heightened amygdala activity in both MDD and OCD patients, which implied that it plays a role in the brain mechanisms of both disorders (46)(47). Based on magnetic resonance imaging, it has been shown that the amygdala volume in patients suffering from OCD or MDD is smaller than in healthy controls. In MDD research it has been found that the difference in volume between medicated MDD patients and controls is much smaller, which means that antidepressants may affect neuronal degradation which possibly underlies the development of MDD (47).

Another part of the limbic system that has been associated with both OCD and MDD is the hippocampus. Like the amygdala, MRI studies have shown that the hippocampal volume is also decreased in both disorders. Another similarity is that the difference in volume is smaller between medicated MDD patients and healthy controls compared to unmedicated

patients suffering from MDD (48)(49). Both these findings suggest that neuronal degradation in the limbic system might be one of the causes behind the development of both OCD and MDD, which makes sense since this system is involved in emotional and behavioural processing.

The hypothalamic-pituitary-adrenal (HPA) axis is a system composed of the hypothalamus, the pituitary gland, and the adrenal glands. Feedback interactions between these organs play a role in stress as well as emotion regulation and response so it is considered to be involved in many different stress-related disorders. Hyperactivity of the HPA axis has been found in both OCD and MDD, and it seems to stem from abnormalities in the regulation of the axis. Although it has not been thoroughly researched yet, this axis possibly plays a role in comorbidity of MDD and OCD (50)(51).

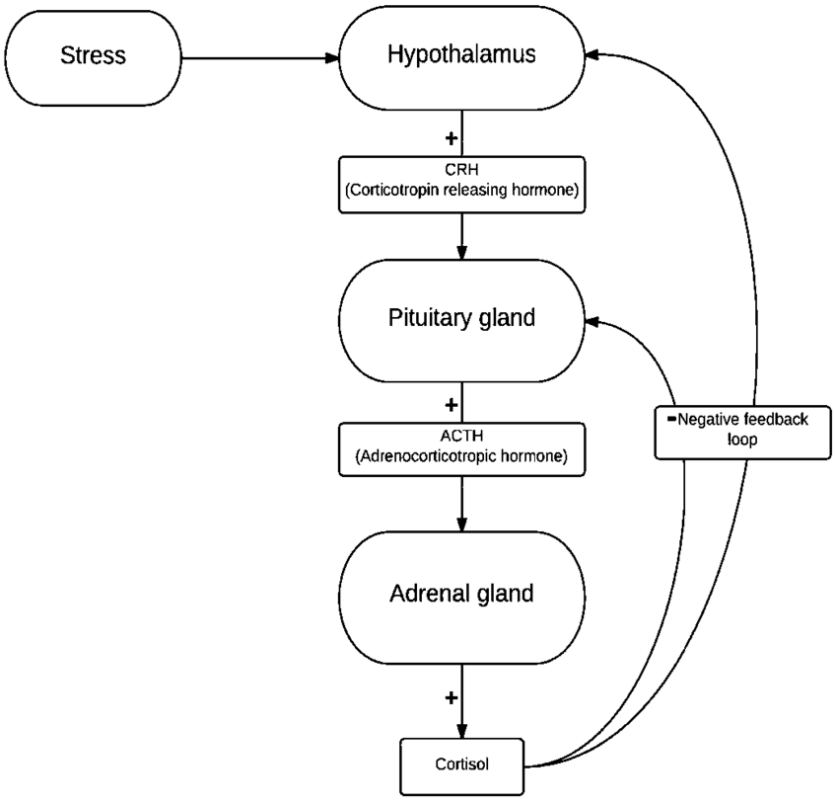

Figure 2. **Simplified schematic illustration of the HPA axis negative feedback loop. Taken from Ha et al 2016** (52)

As described earlier, both disorders have been shown to have abnormalities in neurotransmission. In the case of MDD, the most well-known hypothesis is the 'monoaminergic hypothesis', which states that MDD occurs in part as a result of 5-hydroxytryptamine synaptic deficiency caused by increased degradation of monoamine oxidase. 5-HT is a serotonin monoamine transmitter and thus involved in the serotonin reuptake mechanism, which is the target of selective serotonin reuptake inhibitors (SSRIs), the most commonly used antidepressants for treating both OCD and MDD. This hypothesis is no longer considered to be sufficient to explain MDD development, but remains relevant. A similar theory exists also about OCD, but is not backed up by as much data. Another theory proposes the dopaminergic system as a possible contributor to MDD, as a dopamine receptor D_3 has been shown to be downregulated in depression. Since dopamine has a role in stereotypic behaviour, dopaminergic system is a very important candidate when researching OCD mechanisms. Glutamate transmission abnormalities are another possible mechanism behind both MDD and OCD and show a lot of promise in future research (3)(53).

4.2. Shared genes

4.2.1. 5-HTTLPR

Solute carrier family 6 member 4 (*SLC6A4*) is a gene located on chromosome 17 and codes for an integral membrane protein 5HTT, involved in serotonin reuptake. It is a sodium-dependant serotonin transporter that terminates serotonin action by transporting it from the synaptic spaces into presynaptic neurons to be recycled and is in that way involved in serotonin regulation (53). Since this pathway has been shown to be altered in both OCD and MDD *SLC6A4* is a gene of interest when researching genetics of both these

disorders. A functional polymorphism of the *SLC6A4* gene, 5HTTLPR, has most been associated with both OCD and MDD. It is a 44 bp insertion/deletion polymorphism which results in 14-repeat short allele (S), which contains the deletion and a 16-repeat long allele (L), which contains the insertion. The alleles have different transcriptional activity, which results in differences in 5HTT expression (54).

When reviewing the most recent findings about 5-HTTLPR and MDD the S allele had a higher genotypic frequency overall, as the L/L genotype is present in 29-43% of Caucasians and 1-13% of Asians. The S allele is considered to decrease transcription of the 5HTT promotor gene which results in reduced 5HTT expression and lower serotonin uptake (55). The alleles also have different effect on the nervous system of the individual. SS homozygous individuals suffering from either MDD or OCD both showed smaller hippocampal volumes than healthy controls, a characteristic that has previously been associated with both disorders (56)(54). The SS genotype and the S allele itself have also been linked to suicide attempts, as studies have shown that the individuals with the S allele have a higher risk of attempting suicide (57). The L allele can be subdivided into L_A and L_G, based on the A to G substitution on the L_G SNP, which is considered to also reduce the efficiency of serotonin reuptake. The L_A allele has been shown to play a role in OCD development, as it is twice as common in Caucasians with OCD than in controls and the L_AL_A genotype has a twofold effect on the relative risk of developing OCD (54)(58). Studies show that polymorphism of the 5-HTTLPR affect brain morphology of MDD and OCD patients in different ways and that it is likely to be involved in development of both disorders.

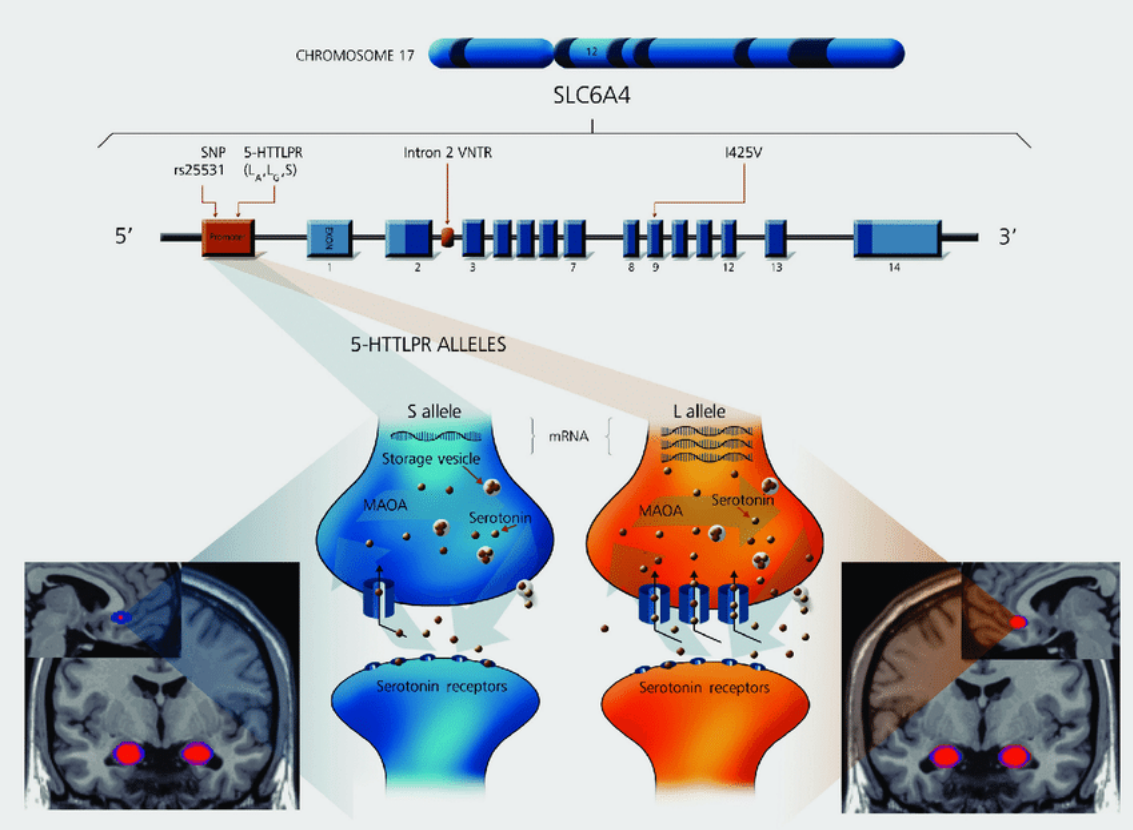

Figure 3. **Different effects of 5-HTTLPR alleles on serotonin transportation. Taken from Mattina et al 2020** (59)

4.2.2. HTR2A

The 5-hydroxytryptamine receptor 2A coding gene, *HTR2A*, is a gene involved in serotonergic neural transmission and has been researched in relation to both OCD and MDD. The serotonin receptor it codes for is also a target of SSRIs. The gene is located on the long arm of the chromosome 13 and its mutations have previously been associated with various mental disorders such as schizophrenia and bipolar disorder (60).

A synonymous substitution on exon 1 of this gene, T102C, defined by a T to C transition, has been found to be of importance in OCD. In OCD patients with the T allele, a higher level of the 5-HT_{2A} receptor protein in cortical tissues has been observed (61). Although more research is needed to confirm these

finding, this polymorphism appears to be associated with females with early onset OCD (62)(63). The same SNP was researched in relation to MDD but no significant association to MDD susceptibility was found (64)(65).

Another polymorphism of this gene, A1438G, has been associated with both disorders. This SNP is thought to affect the transcription of the gene and in that way alter the number of serotonin receptors. In OCD patients, the A allele is more common, and it is thought it may be characteristic to certain subtypes of the disorder, such as early onset or with severe symptoms, although current research is still inconclusive (62).

The A1438G polymorphism has also been implicated in susceptibility to MDD, but due to contradictory study results it is not clear which allele is responsible for it. Some studies have found that the A allele is associated with MDD while others maintain it is the G allele (64)(66). Nevertheless, the connection between this polymorphism and MDD susceptibility has been repeatedly confirmed. As a gene involved in serotonin transmission, *HTR2A* was reasonably considered a candidate gene when researching MDD and OCD overlap. The findings regarding its SNPs and their possible roles in underlying genetic pathways of the disorders confirm that this gene is associated with susceptibility to both MDD and OCD, and future research might find it relevant in term of their comorbidity.

4.2.3. FKBP5

The *FKBP* prolyl isomerase 5 gene, located on chromosome 6, is a protein coding gene. The protein is a member of the immunophilin protein family and is involved in immunoregulation and other cellular processes involving protein folding (67). It is also responsible for determining the sensitivity of the glucocorticoid receptor (GR), which plays a role in the regulation of HPA axis activity. Cortisol, which activates the GR consequently induces the *FKBP5*

transcription, while increased levels of the protein decrease the affinity of the receptor resulting in negative feedback loop.

This gene and its SNPs have been associated with various stress-related mental disorders, with MDD as one of them. In MDD, the methylation of *FBKP5* seems to be important when considering HPA axis functionality. Lower levels of methylation of this gene have been associated with smaller volume of grey matter in the part of the prefrontal cortex connected to modulation of negative emotion. Lower methylation levels have also been correlated with high stress exposure in early life in individuals carrying the T allele of the rs1360780 SNP. The T allele of this polymorphism is considered to be a moderate-risk allele as it is found more commonly in individuals suffering from MDD than in healthy controls, and affects the transcription pattern of *FKBP5* (68)(69).

Another SNP on the *FKBP5* locus relevant in MDD development is rs9470079-A. It also contributes to higher expression of *FKBP5,* resulting in higher level of GR binding. In this way, it affects the HPA axis negative feedback regulation system. This polymorphism is also a great candidate when researching OCD, as HPA axis irregularities have also been reported as one of its many mechanisms and it is a stress-related disorder. It decreases the systems negative feedback and contributes to the development of both these disorders. Although the exact mechanism is not yet known, *FKBP5* and its SNPs show great promise for future studies of stress-related mental disorders (50)

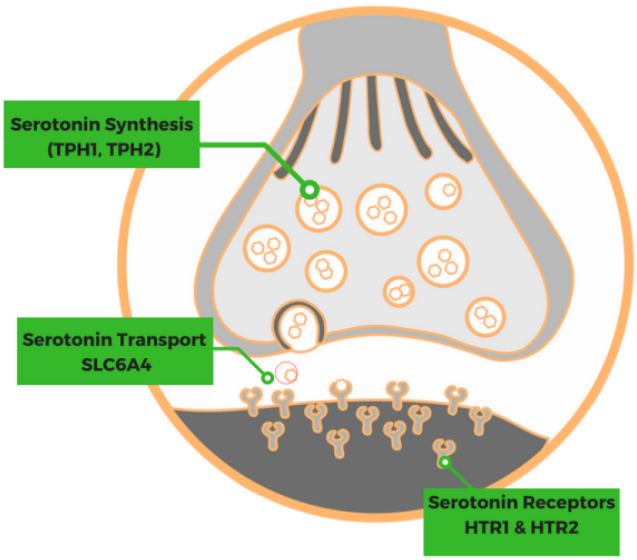

Figure 4. **The role of TPH2, SLC6A4 and HTR2A in serotonin transportation. Taken from Moon 2021** (70)

4.3. Shared treatment effects

Since they share a number of brain mechanisms and are often co-diagnosed, it is unsurprising that OCD and MDD share some aspects of their treatment as well. They are both treated with psychotherapy, which varies in focus and methods, and pharmacotherapy, which is based on molecular mechanisms underlying each disorder. Both approaches have been shown to achieve best results when combined (45).

When reviewing the genetic overlap between these disorders it is clear that genes like *SLC6A4* and *HTR2A* affect the serotonergic pathways in both OCD and MDD, so it is logical that serotonin transmission, and especially serotonin reuptake, are a target when treating both disorders. Drugs used to treat MDD, also known as antidepressants, most commonly target monoaminergic transmission. Selective serotonin reuptake inhibitors (SSRIs),

which show broad-spectrum efficiency, act as antagonists to the 5-HTT serotonin transporter and as a result block serotonin reuptake. The same group of drugs is used as the most common pharmacological treatment for OCD as well, but are usually prescribed at higher doses. Among the most commonly used SSRIs for treating MDD and OCD are fluoxetine, sertraline and citalopram. Clomipramine, a non-selective serotonin reuptake inhibitor, better known as a SNRI (serotonin and norepinephrine reuptake inhibitor) is also highly efficient at treating OCD, but SSRIs have been shown as generally safer and more tolerable (3) (4) (13).

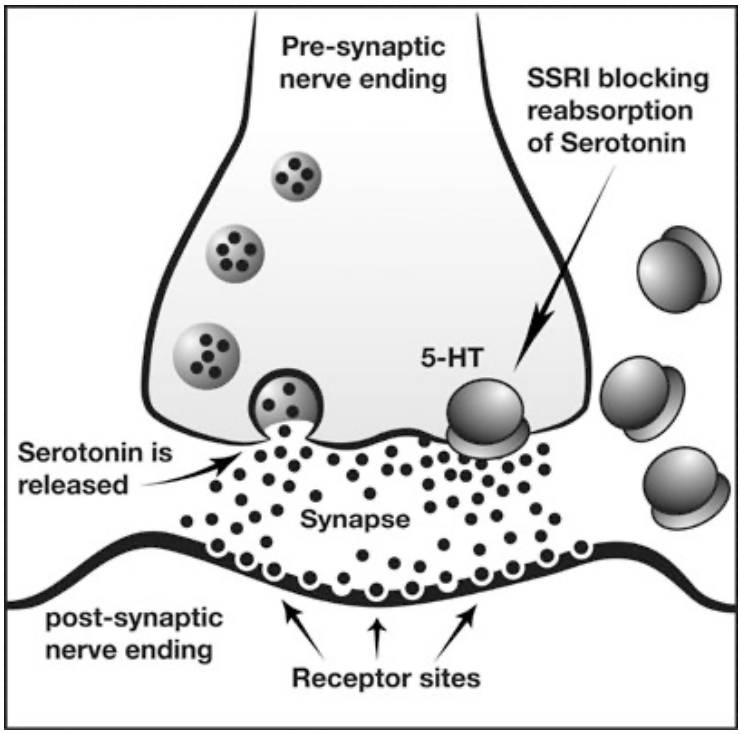

Figure 5. **Schematic illustration of the role of SSRIs in serotonin reuptake. Taken from Lattimore at al 2005** (71)

A large number of both OCD and MDD patients seem to have treatment resistant types of these disorders. In such cases new treatment strategies are needed, such as neuromodulation. Neuromodulation is used to treat both

treatment resistant MDD and OCD and it includes non-invasive and invasive approaches (3)(4).

Repetitive transcranial magnetic stimulation is a non-invasive method which modulates neuronal activity using electric current induced by a magnetic coil positioned over patient's head. It is considered an alternative for patients who have at least two failed antidepressant treatment attempts (3)(4).

Transcranial direct current stimulation is a neuromodulation method which typically applies a weak current to the patients' scalp with only a fraction of the current entering patients' brain via scalp electrodes positioned over target areas. This method is still being studied but initial results show greater promise for treating OCD than MDD (3)(4).

Deep brain stimulation is another method that involves the implantation of a pulse generator that is connected to two stimulating electrode wires located in specific regions of the brain. The implant can then stimulate neighbouring brain regions. This approach is used only on very severe cases of OCD and MDD and although the results are promising it still needs further research and evaluation (3)(4)(45).

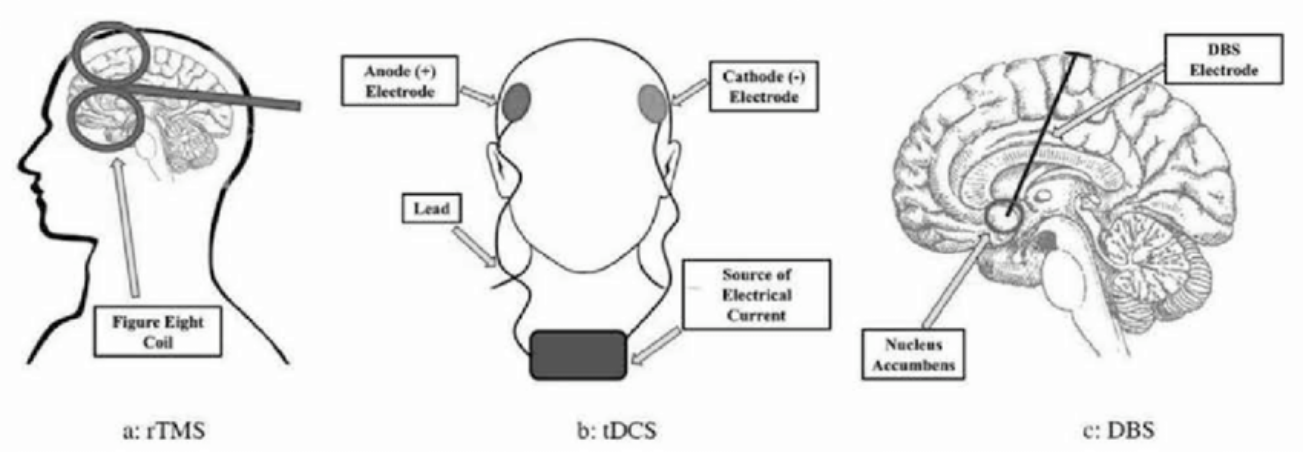

Figure 6. **Simplified illustration of different neurostimulation methods (repetitive transcranial magnetic stimulation, transcranial direct current stimulation and deep brain stimulation). Taken from Kumral et al 2020** (72)

5. Conclusions and future outlook

OCD and MDD are highly comorbid disorders, as up to 39% of OCD patients suffer from MDD as well. Both disorders are heterogenic and polygenic, leading to the question "is there an overlap in genetic background of these two disorders?". By reviewing multiple studies on this subject, it became clear that in order to get the most complete picture of this topic, multiple aspects should be taken into consideration.

In order to find common genes of interest the overlap of underlying biological pathways should be considered. Based on known risk genes associated with both OCD and MDD, neurotransmission pathways are highly affected in both disorders. When it comes to patients with MDD and OCD, both have been shown to exhibit smaller volumes of amygdala and hippocampus, which points to neuronal degradation in the limbic system. Also, abnormalities of the HPA axis regulation have been associated with both disorders, meaning this is also a mechanism which affects the development of OCD and MDD.

Although not many shared genes have yet been discovered a few of them show promise or future research. One of them is *SLC6A4*, a gene encoding a serotonin transporter. Alleles of this gene, especially 5-HTTLPR, have been associated with both disorders and it seems to influence the serotonergic pathway and hippocampal volume. Another such gene is *HTR2A*, also encoding a receptor in the serotonin transportation pathway. Different polymorphisms of this gene have been associated with OCD and MDD, and despite contradictory study results, this gene continues to be of interest when researching the overlap between these disorders. *FKBP5*, a gene encoding a protein responsible for sensitivity of GR involved in the HPA axis activity is also potential gene of interest when researching the overlap of these disorders. The levels of methylation of this gene and its SNPs have been associated with MDD, and since the HPA axis is involved in OCD development,

it is considered relevant in relation to that disorder as well. Nevertheless, more research is needed to confirm this.

Another aspect that should be taken into consideration to fully understand the similarities between OCD and MDD are the shared treatment effects. Both OCD and MDD patients seem to respond to SSRIs, although many patients seem to have treatment resistant types of these disorders. In those cases, new approaches such as neuromodulation are used. This includes repetitive transcranial magnetic stimulation, deep brain stimulation and transcranial magnetic stimulation.

Findings regarding the overlap in genetics of comorbid disorders help us understand why they are so often co-diagnosed, as well as how to approach future treatment development. Some of the genes mentioned in this review, such as *SLC6A4*, are already known to be of significance when it comes to the overlap between MDD and OCD, while others are still to be thoroughly researched but show great promise. Since the currently known genes, discussed in this review, are mostly involved in the serotonergic pathway, this suggests that future studies will probably be able to find out how exactly the polymorphisms of these genes impact the transmission of serotonin and how that reflects in the symptoms a patient is experiencing. For others, like *FKBP5* where research is still very limited and the findings are not yet definitive, research might develop in different directions. We can expect a number of new studies which will help better explain their role in HPA axis irregularity and how does that mechanism even relate of the development of OCD and MDD. By understanding this, new genes, also involved in HPA axis regulation, might be discovered as relevant to these disorders. Most importantly, future studies will bring us more definitive findings about the reason behind the comorbidity of these two disorders. Although they share a number of different factors, there is still not a precise enough explanation of why exactly these disorders are so commonly co-diagnosed.

Understanding the physiological and genetic background of these disorders, as well as how they overlap, will enable us to have a better approach to developing more efficient drugs and other types of treatments for individuals which suffer from both OCD and MDD. These would then target specific genes and proteins in order to maximise their benefits, as well as minimise possible side effects insuring a more effective treatment. By finding the specific mechanism of serotonin transport and reuptake altered in both disorders a new type of SSRI might be developed. Another possible direction in drug research could be a drug targeting and regulating the glucocorticoid receptor involved in the regulation of the HPA axis. Although findings are still limited, it seems like the near future might bring new and more definitive information which could then be used to help numerous people and shed more light on these complex disorders.

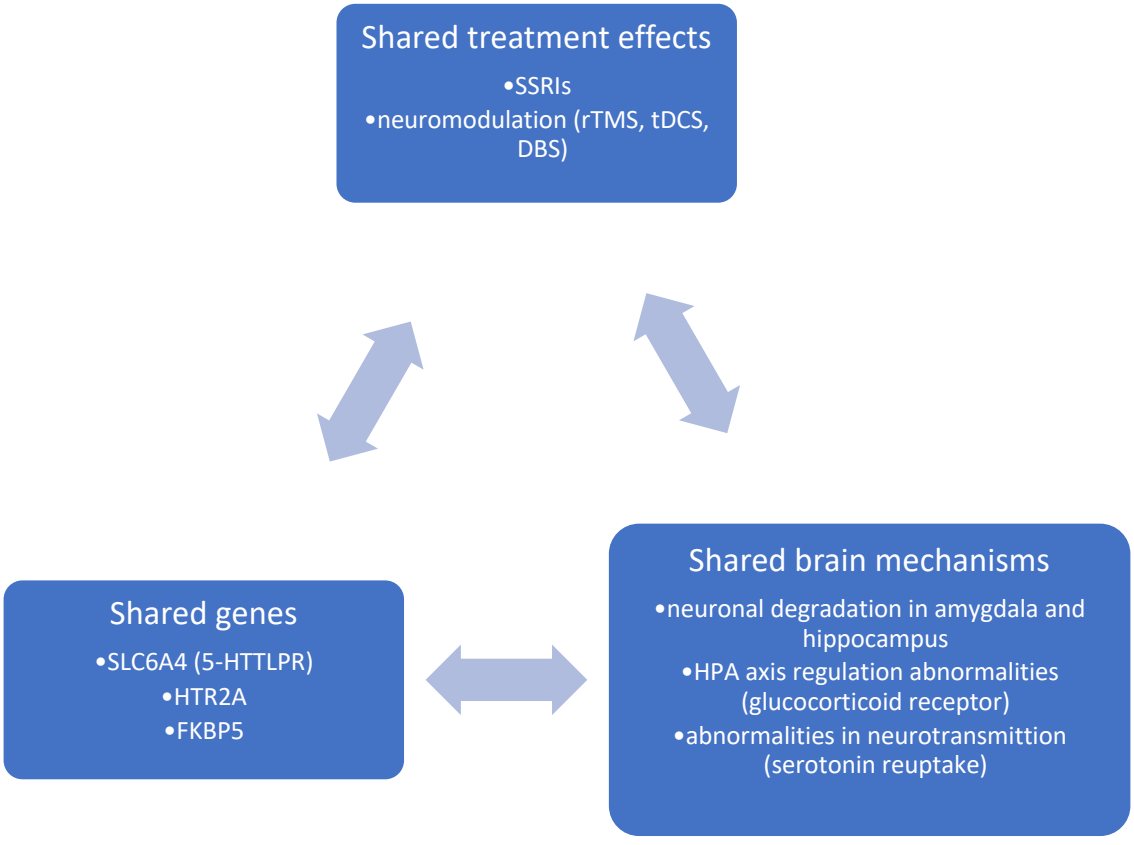

Figure 7. **The three aspects of the overlap between OCD and MDD**

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