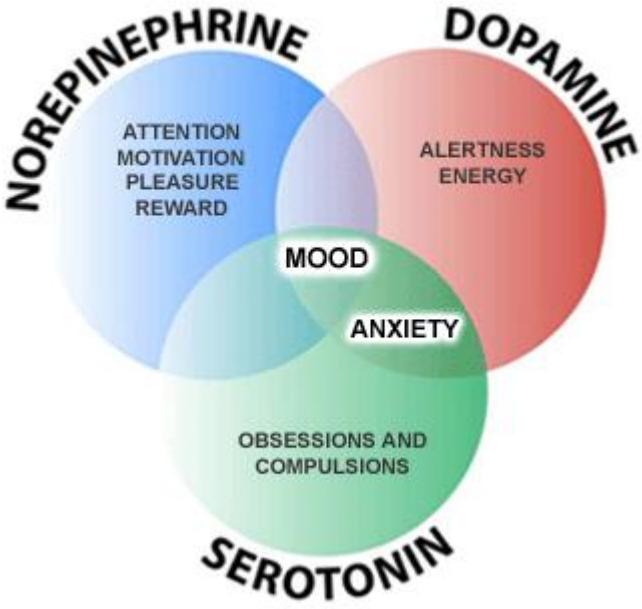
Universiteit Utrecht

Neuroscience & Cognition

UNRAVELING THE INTERACTIONS BETWEEN SEROTONIN AND DOPAMINE IN THE COMPULSIVE AND IMPULSIVE BEHAVIOUR UNDERLYING OBSESSIVE-COMPULSIVE DISORDER

T. Visser, M.S. Kops, S.M. Korte

Division of Pharmacology, Department of Pharmaceutical Science, Faculty of Science, University of Utrecht, Utrecht, The Netherlands



Master Thesis

Tiny Visser

0471356

Neuroscience and Cognition

Overview

Chapter 1: Background

1.1 Aim of the thesis

A lot is known about Obsessive-Compulsive Disorder (OCD) so far. It is known what obsessions and compulsions are, what brain regions are involved and even a treatment is available. So the aim of this thesis could be a summing up of all the obtainable data present in literature. But it is not like that. When looking closer into the information available about OCD, it is actually not a very well known disorder. Why do SSRI's work and what is their precise mechanism of action in the brain? Why is adjuvant prescription of antipsychotics useful and what is the exact role of dopamine in this therapy? Many questions remain unanswered about the treatment. And then there is the impulsive behaviour seen in OCD patients. What is the difference between compulsive and impulsive behaviour and how can understanding of this matter contribute to more insights into the disorder, as well as improved treatment?

This thesis will not provide the exact answers to all these questions. But an in-depth analysis will be given about the problems addressed in the previous section and hopefully enlighten the subject to those curious about OCD in every aspect. In this thesis it is made important to discuss the findings from literature. Why are these conclusions relevant and what is the consequence towards future directions? Starting with an introduction about the disorder, step by step more will be revealed about the roles of serotonin, dopamine, compulsive and impulsive behaviour, always bearing in mind the question: how can this be linked to a better treatment of this debilitating disorder?

1.2 Prevalence, definition and symptoms of Obsessive-Compulsive Disorder

Obsessive-Compulsive Disorder (OCD) is a severe psychiatric disorder, affecting 2-3% of the population (Kopell, Greenberg, & Rezai, 2004) (Nuttin et al., 2008) (Aouizerate et al., 2004). Intrusive thoughts (obsessions) cause extensive fear that patients try to relieve by certain repetitive, ritualistic behaviour (compulsions) (Aouizerate, Guehl et al., 2004). The most common compulsions are checking, ordering, praying, counting, touching, collecting, hoarding, washing and cleaning (Math & Janardhan Reddy, 2007). Compulsions vary per person and are often carried out to neutralize the anxiety caused by the obsessions, or until it 'feels right' (Björgvinsson, Hart, & Heffelfinger, 2007). According to DSM-IV, OCD is classified as an anxiety disorder and certain criteria have to be met for correct diagnosis (American Psychiatric Association, 2000) (emedicine, 2010), *see table 1*.

Table 1: Criteria for obsessions, compulsions and other criteria that have to be met for correct diagnosis with obsessive-compulsive disorder (American Psychiatric Association, 2000)(emedicine, 2010)

Criteria for obsessions	Criteria for compulsions	Other criteria for OCD
* Recurrent and persistent thoughts * Craziness of unwanted thoughts are recognized * Not simply excessive worries about real-life problems * Attempt to suppress, ignore or neutralize * Product of own mind	* Repetitive behaviours or mental acts in response to an obsession or according to rules that must be applied rigidly * Aim to prevent or reduce distress or prevent dreaded event or situation	* Recognizing obsessions or compulsions are excessive or unreasonable * Causing marked distress * Not due to the direct physiologic effects of a substance or a general medical condition

1.3 Pathophysiology of OCD

Development of OCD is influenced by learning principles, as well as it is related to biological, genetic and familial factors (Björgvinsson et al., 2007). Learning principles are explained by a two-factor learning model for acquisition and maintenance of obsessive-compulsive symptoms (Markarian et al., 2010). Following this model, OCD develops via classical conditioning (a neutral stimulus is paired with an aversive stimulus which elicits a conditioned fear response) and is maintained via operant conditioning (compulsions or rituals executed to neutralize obsessions which leads to reduced anxiety, the negative reinforcer) (Markarian et al., 2010).

According to several studies, the metabolic activity of the OFC and striatum appear to be higher in OCD patients compared to healthy controls. Besides, during symptom provocation an even greater increase of activity was found. After successful treatment, a decrease was seen (El Mansari & Blier, 2006).
Therefore, brain areas appearing to be involved in OCD are the ventral prefrontal cortex (specifically the medial orbito-frontal cortex and subgenual anterior cingulate cortex), dorsal/ventral striatum, thalamus and ventral globus pallidus (Rauch et al., 2006), *see figure 1*.
Cortico-striato-thalamocortical interactions are implicated in the pathogenesis of OCD due to its symptoms and response to treatment. Clinically and genetically related to OCD is Gilles de la Tourette, a disorder characterized by multiple physical tics (Kopell et al., 2004). Also in that disorder, a central role of the basal ganglia is suggested *(see chapter 2 for an explanation of anatomy and function of the basal ganglia)* (Kopell et al., 2004).

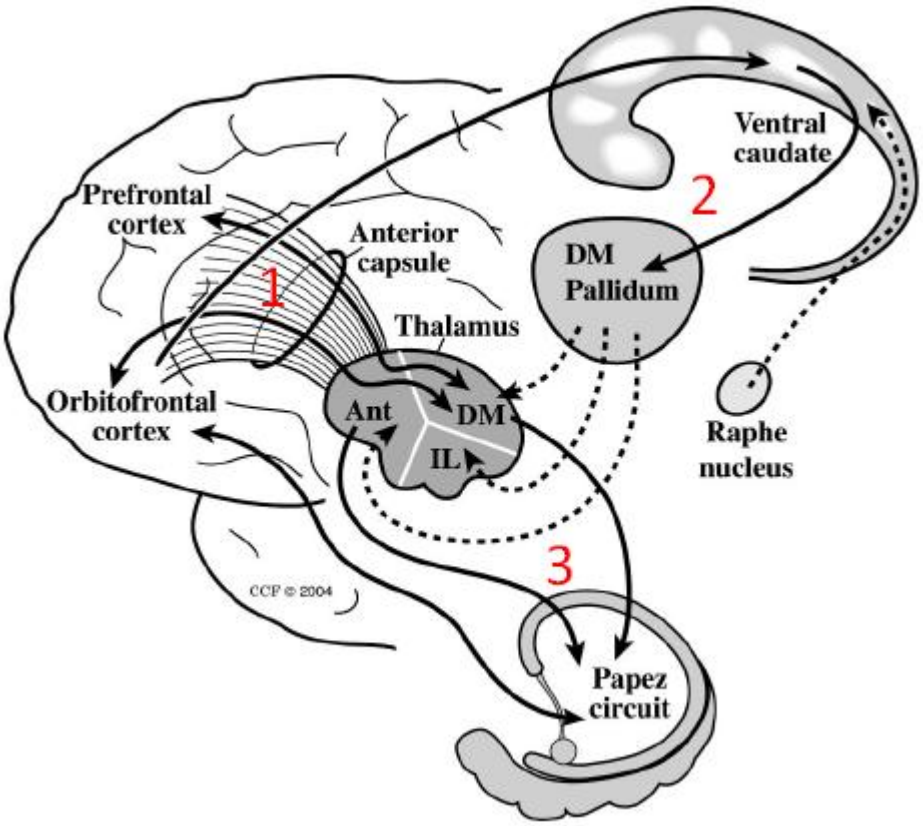


Figure 1: Schematic anatomy of the OCD neural circuitry (Kopell et al., 2004). Three circuits (loops) seem to be mainly involved in the disorder. Circuit 1 is a positive feedback loop involving the orbital and prefrontal cortex and the dorsomedial thalamic nucleus, by way of the anterior limb of the internal capsule. Circuit 2 comprises the orbitofrontal cortex (OFC) cortico-striato-thalamocortical loop; involving the OFC, ventral caudate, dorsomedial pallidum and intralaminar (IL), anterior (ant) and dorsomedial (DM) thalamic nuclei. Circuit 3 consists of the limbic system and circuit of Papez (with projections from the anterior cingulate cortex (ACC) to the nucleus accumbens (NAcc) region of striatum) (Kopell et al., 2004)

When closely examining the three components from *figure 1*, obsessive-compulsive symptoms occur when an abnormal positive feedback loop develops in the excitatory orbitofrontothalamic neuronal pathway. This then is inadequately inhibited by the combination of the striatum / dorsomedial pallidum / thalamus (Kopell et al., 2004). When the latter activity is decreased due to an imbalance in the direct and indirect pathways *(see chapter 2)*, this results in an increase of the orbitofrontothalamic pathway. Expectedly, either increasing the modulating loop (the second) or decreasing the excitatory loop (the first) results in a decrease of obsessive-compulsive symptoms (Kopell et al., 2004).

1.4 Current treatment

The prescribed treatment for OCD consists in most cases of behavioural therapy with or without pharmacotherapy (Björgvinsson et al., 2007) (American Psychiatric Association, July 2007).

Behavioural therapy is a first-line treatment and should always be considered. The most common is exposure therapy, also called 'exposure and response (or ritual) prevention' (ERP). By means of ERP therapy, which can be challenging and causing great distress, the patient is exposed to symptom triggers of increasing intensity, while suppressing the usual ritualized response (American Psychiatric Association, July 2007).

Pharmacotherapy consists of selective serotonin reuptake inhibitors (SSRI's such as fluoxetine, fluvoxamine, paroxetine, sertraline) and serotonin norepinephrine reuptake inhibitors (SNRI such as venlafaxine) or a tricyclic antidepressant (TCA such as clomipramine) (American Psychiatric Association, July 2007). However, the role of norepinephrine is considered submissive to the role of serotonin and will be considered in the *future directions*. The prescription of SSRI's (Jackson, Morton, & Lydiard, 1994), either with or without adjuvant therapy of antipsychotics (atypical antipsychotics such as clozapine, olanzapine, quetiapine, risperidone), suggests a role of the serotonin (5-HT) system in the disorder. SSRI's prevent serotonin from being pumped back into the presynaptic neurons, therefore increasing its availability in the synapse and postsynaptic neurons, *see figure 2* (Blier, Habib, & Flament, 2006) (oknation, 2010).

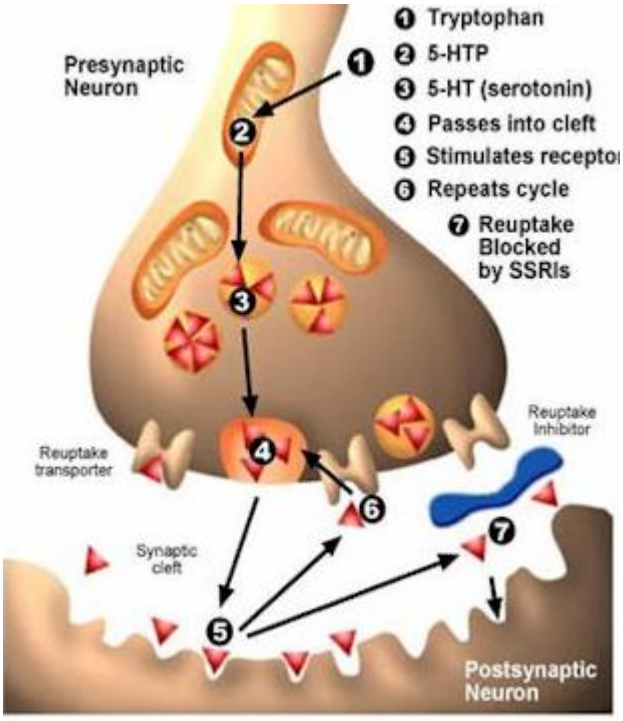


Figure 2: Illustration of conversion to from tryptophan to serotonin and the mechanism of SSRI's (oknation, 2010)

A measure for rating the severity of obsessive and compulsive symptoms separately is the Y-BOCS (Yale-Brown Obsessive-Compulsive Scale) (Goodman, Price, Rasmussen, Mazure, Delgado et al., 1989; Goodman, Price, Rasmussen, Mazure, Fleischmann et al., 1989). It is also used to determine improvement during treatment (Goodman, Price, Rasmussen, Mazure, Delgado et al., 1989; Goodman, Price, Rasmussen, Mazure, Fleischmann et al., 1989).

Recently, increasing attention is devoted to the role of the dopamine system in OCD. Prescription of antipsychotics in combination with antidepressants seems to improve the symptoms in patients not responding to the individual drugs (Choi, 2009). Therefore, a closer look has to be taken upon both serotonin and dopamine and their role in OCD. The next chapter is dedicated to the serotonin theory, dopamine involvement and the link between these neurotransmitters.

Chapter 2: The role of serotonin and dopamine signalling in OCD

2.1 Serotonin theory for OCD

Serotonin (5-hydroxytryptamine; 5-HT) is released in the brain from the neurons of the raphe nuclei and has functions in a wide range of brain areas, including the hippocampus and amygdala (Jackson et al., 1994). Serotonin is primarily known for its role in modulation of mood, but has several other functions (Weber et al., 2009). Serotonin is a monoamine neurotransmitter and the main source for release in the brain are the neurons of the raphe nuclei. From here, almost every part of the central nervous system is reached. The action of serotonin is stopped after the uptake of 5-HT from the synapse through a monoamine transporter (SERT) on the presynaptic neuron. Reuptake can be inhibited by various agents like the aforementioned tricyclic antidepressants and SSRI's, but also drugs like ecstasy and cocaine will increase serotonin levels in the synapse (Pum, Carey, Huston, & Müller, 2007). *See figure 3* for a detailed overview of a serotonin neuron (El Mansari & Blier, 2006).

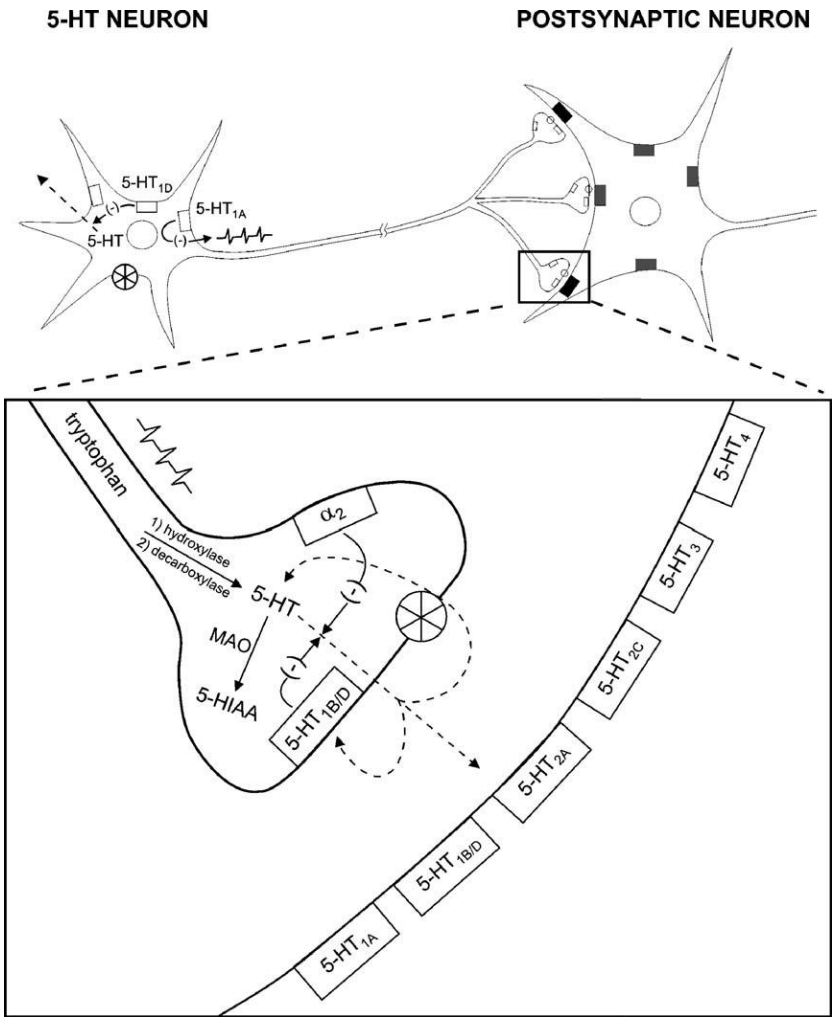


Figure 3: Presynaptic and postsynaptic modulators for serotonin neurotransmission. Serotonin receptors located on the serotonin neurons exert a negative feedback. This negative feedback regards neuronal firing in the case of the 5-HT_{1A} autoreceptor, and serotonin release in all other cases. Different serotonin receptors are located in distinct areas of the (body and) brain and exert different functions. MAO=monoamine oxidase (deamination/breakdown of monoamines like serotonin) (El Mansari & Blier, 2006)

Based on the efficacy of SSRI's as a treatment, serotonin as a neurobiological factor seems to play an important role in OCD. However, only few data support a primary involvement of brain serotonergic systems in the pathogenesis of this disorder (El Mansari & Blier, 2006). Due to the inhibition of the serotonin reuptake process, the desired effect in reduced OCD symptoms is seen (El Mansari & Blier, 2006). This is realized via effects of SSRI's on presynaptic and postsynaptic serotonin receptors in brain regions involved in OCD.

To explain what is mentioned above, it first has to be realized that there is a difference between treatment effect in depression and OCD. The latency period from initiating a trial to the time of response is longer in OCD patients than in the patients suffering from major depression. The latter group usually responds to SSRI treatment in 2-6 weeks, whereas response in OCD patients may take up to 10-12 weeks (Dougherty, Rauch, & Jenike, 2004). The clinical observation that the maximal therapeutic effect is obtained after a longer delay in OCD patients is consistent with a 3-week paroxetine treatment study (El Mansari, Bouchard, & Blier, 1995). In this preclinical study, an enhancement effect of serotonin release on the frontal cortex and the hypothalamus of guinea pig was found, but not in the OFC or in the head of the caudate nucleus (El Mansari et al., 1995). After an 8-week paroxetine treatment study, also in the OFC an increase in (evoked) serotonin release was found, but it was still unchanged in the head of the caudate nucleus; autoreceptor sensitivity was unaltered (El Mansari et al., 1995). On the other hand, fluoxetine (like paroxetine an SSRI) had no effect on these regions after 3 and 8 week treatment studies, which can be due to fluoxetine having no effect on the modification of the sensitivity of the serotonin autoreceptor (receptor located on presynaptic neuron), but also to the dosage which appeared to be too low (El Mansari et al., 1995). This study then indicates the reason why there is a delay in response to treatment in OCD patients; instead of obtaining the desired effect of SSRI's after a maximum of six weeks, no improvement is observed in the 'OCD-regions' of the brain in this amount of time when administering the treatment. It requires more time to also activate these systems and therefore, the wanted effect is only seen after a 10-12 weeks, if found at all.

Also, in treating OCD, a higher dosage is given compared to patients suffering from depression (Dougherty et al., 2004). One could suggest that a higher dose of SSRI's

inducing a larger degree of reuptake inhibition plays an essential role in the desensitization of the serotonin autoreceptor (El Mansari & Blier, 2006).

Also postsynaptic effects are seen after treatment with SSRI's. Not only presynaptic autoreceptors, but postsynaptic serotonin receptors in the OFC could be altered after prolonged SSRI administration. However it is suggested that the activation of 5-HT_2 receptors mediates the effect of SSRI administration (long-term); the sensitivity of these receptors remains unchanged (El Mansari & Blier, 2006).

As mentioned before, support for the serotonin theory for OCD consists mainly of the efficacy of SSRI's in the treatment of this disorder. Another mechanism via how this works is proposed. Patients seem to have excessive baseline activity of the excitatory glutamatergic neurons in the OFC. It is suggested that serotonin inhibits these neurons, which results in an increased release of serotonin which then leads to a decline in symptoms (Markarian et al., 2010). In this theory, the enhanced prefrontal glutamatergic activity, or glutamate dysfunction, leads to overactivity in both direct and indirect orbitofrontal-subcortical circuits (Davidson & Bjorgvinsson, 2003). This is interesting because in this way, both 'behaviourally activated symptoms' like cleaning and repetition as well as 'behaviourally inhibited symptoms' like slowness are accounted for (Davidson & Bjorgvinsson, 2003). On the downside, the glutamate-modelling drug lamotrogine has been tested, but to date not been found useful in alleviating OCD symptoms (Ramesh Kumar & Khanna, 2000).

2.1.1 Evidence based on treatment and animal models

There is, so far, no clear animal model for OCD that has good face (phenomenological similarity between the animal model and the disorder it models), predictive (performance in the experimental test predicts performance in the modelled human phenomenon) and construct validity (whether a scale measures or correlates with the theorized psychological construct that is supposed to measure) (Boulougouris, Chamberlain, & Robbins, 2009). However, many animal studies model one or more endophenotypes that can be linked to (obsessive) compulsive behaviour. Hence the 5-HT_{2C} receptor knock-out mouse, which exhibits compulsive-like behaviours (Chou-Green, Holscher, Dallman, & Akana, 2003). The mice in this study showed distinct orderly chewing patterns and also exhibited reduced habituation of head dipping activity (Chou-Green et al., 2003).

Another study examines the role of the striatum in compulsive behaviour, especially in rats with lesions in the OFC (Schilman, Klavir, Winter, Sohr, & Joel, 2010). In the 'signal attenuation model', rats show compulsive behaviour by means of attenuating a signal indicating that a lever-press response was effective in producing food (Joel & Avisar, 2001). Lesions in the rat OFC leads to a higher amount of compulsive lever-pressing (it is named compulsive, since it is suggested to resemble the excessive and unreasonable behaviour seen in OCD patients), whereas paroxetine interferes with this increase (Joel, Doljansky, Roz, & Rehavi, 2005) (Joel, Doljansky, & Schiller, 2005). Keeping in mind the model of compulsive lever-pressing, the interaction between the OFC, striatum and the serotonergic system was further explored (Schilman et al., 2010). It was found that lesions in the OFC decrease the amount of dopamine, glutamate, GABA and serotonin in the striatum. Furthermore, the effect of paroxetine as an anti-compulsive drug was confirmed (Schilman et al., 2010). Overall it was suggested that in a certain population of patients, primary pathology of the OFC can lead to a dysregulation of the serotonergic system in the striatum. This results in compulsive behaviour, which can be neutralized by normalizing the dysfunctional system by means of psychopharmaca (Schilman et al., 2010).

In a different study, the major serotonin metabolite (5-HIAA) was significantly decreased in the cerebrospinal fluid which related to the anti-obsessional response to drug treatment (Thoren, Asberg, & Bertilsson, 1980). Also, serotonin agonists may exacerbate both anxiety and obsessions in patients, proved by the administration of m-CPP (Katz, 1991). However, this study could not be reproduced, which makes the outcome rather unreliable.

2.2 The newly discovered role of dopamine in OCD

There are several limitations to the serotonin theory. Serotonin could be the only neurotransmitter involved in OCD, but questions arise as to why the latency period before the psychopharmaca work is much longer than for instance in the treatment of depression. Also, the doses given are much higher and even then, a substantial number of treatment-resistant OCD patients do not respond to SSRI's (Matsunaga et al., 2009). Although antipsychotics alone have no effect, evidence suggests that, as additional therapy to the SSRI treatment, they have proven benefit in patients and this implicates a possible role of dopamine in the pathophysiology of OCD (Choi, 2009).

Dopamine is a catecholamine neurotransmitter and a precursor of norepinephrine (noradrenaline), which is a precursor of epinephrine (adrenaline). In the basal ganglia *(see below)* dopamine is inactivated via reuptake by the dopamine transporter and then broken down by monoamine oxidase (MAO). In contrast, dopamine present in the prefrontal cortex is inactivated via reuptake by the norepinephrine transporter and then broken down by catechol-O-methyl transferase (COMT).
Dopamine is localized in specific regions of the brain and follows several pathways (Meck, 2006) leading to different functions in the brain, including roles in behaviour, cognition, motivation, punishment, reward, mood, attention and learning (Salamone, Correa, Mingote, & Weber, 2005). The three main pathways are the mesolimbic, mesocortical and nigrostriatal dopamine pathways. The *mesolimbic pathway* transmits dopamine from the ventral tegmental area to the nucleus accumbens (NAcc). Due to the actions of dopamine, the mesolimbic pathway is suggested to be involved in modulating behavioural responses regarding reward (motivation), emotions and reinforcement. The *mesocortical pathway* neurally connects the ventral tegmental area to the frontal cortex. It is also involved in motivation and reward, besides higher cognitive functions as working memory. In the *nigrostriatal pathway*, dopamine projects from the substantia nigra mainly to the dorsal part of the striatum and has, amongst others, its role in production of movement and control of posture. This last pathway is involved in the basal ganglia motor loop (Meck, 2006).

It is suggested that there is a link between OCD and increased midbrain dopamine neurotransmission. This hypothesis, which involves the basal ganglia, is in agreement with the 'hyperactive corticostriatal model', suggesting an imbalance of the direct versus the indirect pathway (Denys, Zohar, & Westenberg, 2004). For clarification, output from the basal ganglia is established via a direct and an indirect pathway (Yin & Knowlton, 2006), *see figure 4*. The direct pathway involves the cortex, striatum, internal globus

pallidus, thalamus and cortex (excitatory pathway). The indirect pathway runs via the cortex, striatum, external globus pallidus, subthalamic nucleus, internal globus pallidus, thalamus and cortex (inhibitory pathway) (Yin & Knowlton, 2006).

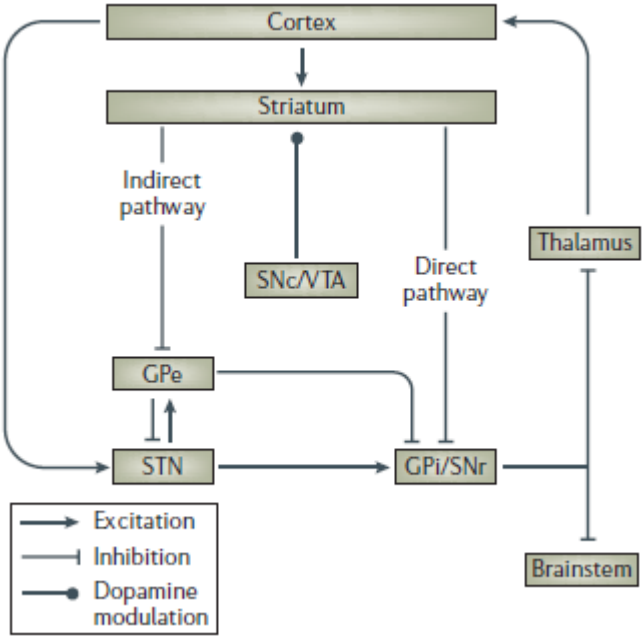


Figure 4: Schematic illustration of the anatomy of the basal ganglia. The direct pathway has an effect on disinhibition of the cortex, whereas the indirect pathway has its effect in inhibiting the cortex. STN=subthalamic nucleus, GPe=external globus pallidus, GPi=internal globus pallidus, SNr=substantia nigra pars reticulate, SNc=substantia nigra pars compacta, VTA=ventral tegmental area. Adapted from (Yin & Knowlton, 2006)

Dopamine receptor families exist in two forms; D_1- and D_2-like receptors. D_1-like receptors (D_1 and D_5) act, for example, in the working memory system. D_2-like receptors (D_2, D_3, D_4) are well known for their role in antipsychotic action and modulation of novelty seeking and impulsivity. Besides, it is known that D_1 receptors preferentially activate the direct pathway and D_2 receptors activate the indirect pathway *(see figure 4)* (Denys, Zohar et al., 2004). Since this is the case, and the density of D_1 receptors is higher in the basal ganglia than the density of D_2 receptors, this will, combined with increased concentrations of dopamine, expectedly result in a dominant D_1-regulated direct circuit. This results in a hyperactive corticostriatal system (Denys, Zohar et al., 2004) and, as discussed above, the hyperactive circuit can be responsible for the repetitive behaviours (Denys, Zohar et al., 2004).

To further dive into the dopamine receptors, several studies can be found related to OCD. As mentioned before, the anterior cingulate cortex (ACC) plays a role in the pathophysiology of the disorder; it is suggested to be hyperactivated during provocation

of symptoms (Olver et al., 2010). Dopamine, acting through D_1 receptors, modulates ACC activity and via imaging studies, it was found that a significantly reduced D_1 receptor binding potential (of a D_1 antagonist to D_1 receptors) is present in OCD patients compared to healthy controls. This leads to the suggestion of mesocortical dopamine input (via D_1 receptors) to play a role in OCD (Olver et al., 2010).

The cortico-striatal(-thalamic) pathway (described in *chapter 1* and again mentioned above) is one of the most accepted neuroanatomical models for explaining OCD symptoms. A study, performed by the same group as the study above, reported reduced binding potential to the D_1 receptors in the caudate nucleus and putamen, again compared to healthy control subjects (Olver et al., 2009). This reduced D_1 binding in the striatum of OCD patients can have its effect on the direct pathway of the cortico-striatal pathway, therefore influencing OCD behaviours (Olver et al., 2009).

Furthermore, dopamine D_2 receptor binding potential in the striatum (left caudate nucleus) was significantly lower in OCD patients compared to healthy controls (Denys, Van Der Wee, Janssen, De Geus, & Westenberg, 2004). This reduced binding potential can then contribute to an overall hyperactive striatal circuit (Denys, Van Der Wee et al., 2004), responsible for repetitive behaviours.

2.2.1 Evidence based on treatment and animal models

Initial evidence for an involvement of dopamine in compulsive behaviour comes from animal models in which either a chronic stimulation of certain D_1-expressing neurons (Campbell et al., 1999) or a chronic treatment with quinpirole (selective $D_{2/3}$ receptor agonist) (Szechtman, Sulis, & Eilam, 1998) induces complex compulsive behaviour, even resembling checking behaviour in the quinpirole study (Szechtman et al., 1998). The well-known and widely used proposed animal model for OCD is that of quinpirole-induced checking behaviour (Szechtman et al., 1998) (Tizabi et al., 2002) (Szechtman et al., 2001). In more detail; in a large open field with small objects in 4 locations, rats that have received quinpirole were inclined to excessively often and rapidly (re)visit two places/objects. On these two locations, the rats performed behaviour that seemed ritual-like and they returned to these objects more rapid than control rats (Szechtman et al., 1998). These 'checking behaviours' were partially attenuated by clomipramine, which is used as a treatment for OCD (Denys, Zohar et al., 2004).
On the other hand, neurochemical studies on the role of dopamine metabolites in (human) patients show no evidence for abnormalities in dopamine function in OCD (Denys, Zohar et al., 2004). However, reasoning for the benefit of atypical antipsychotics in patients is the increase in extracellular dopamine (and noradrenaline) levels in the prefrontal cortex in rats when a combination of olanzapine and fluoxetine was used (Zhang et al., 2000). Quetiapine and fluvoxamine together also lead to an increase of dopamine in the prefrontal cortex and thalamus in rats (Denys, Klompmakers, & Westenberg, 2004).

The 'signal attenuation model', or compulsive lever-pressing model, has also been used to test dopamine receptor antagonists. The behaviour induced by the model is reduced when a dopamine D_1 antagonist is administered (Joel & Doljansky, 2003). The suggestion that D_1 receptors are involved in OCD is confirmed by the treatment with the D_1 antagonist clozapine, an atypical antipsychotic that is used in patients (Davidson & Bjorgvinsson, 2003).

However, as mentioned before, up to date there is not one animal model that resembles OCD in every aspect. It is a complicated disorder and the search for an animal model that covers OCD in all its features has to continue.

2.3 The missing link between the role of these neurotransmitters

The efficacy of treatment with SSRI's has been well established. However, as mentioned before, the delayed onset of response raises doubts as to whether SSRI's function on the serotonin system only. The treatment may act on another system more closely tied to the disorder (Goodman, Barr, McDougle, & Price, 1993). It is also possible that the SSRI's compensate for dysfunction of another system (Goodman et al., 1993). In a study where the SSRI citalopram was used for treating OCD patients, a reduction in the serotonin transporter density was found in the midbrain pons area, together with an increase in dopamine transporter availability, both measured by single photon emission computed tomography (Pogarell et al., 2005). This suggests a serotonin / dopamine interaction in the mechanisms of the current treatment (Pogarell et al., 2005).

Considering serotonin, there seems to be a prominent role for 5-HT_{2A} and 5-HT_{2C} receptors. Most of the atypical antipsychotics are potent 5-HT_{2A} antagonists and are maximally effective when co-administered in a low doses (Goddard, Shekhar, Whiteman, & McDougle, 2008). This latter observation is probably due to the medial frontal cortex, where high-dose therapy with atypical antipsychotics results in 5-HT_{2A} receptor antagonism, which may act countertherapeutic (Bergqvist, Dong, & Blier, 1999). Besides acting on 5-HT_{2A} receptors, these drugs have a more complex profile that also includes 5-HT_{2C} and, evidently, D_2 receptor antagonism. 5-HT_{2C} receptors appear to play an important role in OCD, based on the fact that 5-HT_{2C} knock-out mice exhibit compulsive behaviour like repetitive chewing on non-nutritive substances (Chou-Green et al., 2003). Taken this evidence together, more attention is devoted to developing treatment strategies in which 5-HT_{2A} receptor antagonists (low doses) or 5-HT_{2C} receptor agonists are used as an augmentation strategy, next to the standard SSRI treatment (Goddard et al., 2008).
Considering dopamine, increased midbrain / basal ganglia dopaminergic neurotransmission seem to be of major importance (Goddard et al., 2008). Atypical antipsychotics have a complex receptor affinity profile (Goddard et al., 2008); monotherapy has no effect in improving OCD symptoms. However, given together with SSRI's, the combination of D_2 receptor blockade and 5-HT_{2A} antagonism (see above) can play a crucial role in the therapeutic effects (Goddard et al., 2008).

Taken together these observations, another study published the effects of risperidone, an atypical antipsychotic, on obsessive-compulsive (OC) symptoms (Alevizos, Lykouras, Zervas, & Christodoulou, 2002). Risperidone has a dual antagonistic effect on 5-HT_2 and D_2 receptors and is effective in patients with OCD, not responding to SSRI's, to relieve

symptoms. However, when given in too high doses, risperidone is reported to produce or exacerbate OC symptoms (Alevizos et al., 2002). Here, the treatment with the antipsychotic was initiated to reduce psychotic symptoms, but it produced OC symptoms not reported in the patients before, or exacerbated OC symptoms already present. It is suggested that these risperidone-induced symptoms are dose-dependent and due to a serotonergic-dopaminergic imbalance (Alevizos et al., 2002). Besides, it is worth mentioning that at low doses, risperidone blocks receptors in the mesolimbic pathway. At higher doses, it blocks receptors in the nigrostriatal dopamine pathway, associated with extrapyramidal side effects like tremors (Alevizos et al., 2002).

Chapter 3: Compulsive and impulsive behaviour

3.1 Compulsive and impulsive behaviour in OCD

As stated in the name of the disorder, OCD has a high compulsive element in it. Summarizing the term compulsivity, 'it represents a tendency to perform unpleasantly repetitive acts in a habitual or stereotyped manner to prevent perceived negative consequences, leading to functional impairment' (Fineberg et al., 2010).
Besides compulsivity, being responsible can also be seen an element in the disorder. 'Responsibility OCD' can be regarded as a different type of OCD in which an individual has an extreme amount of guilt which drives them to perform correct rituals (Phillipson, 2010). However, excessive responsibility, or being afraid to make mistakes for which the sufferers can be blamed, has also been proposed as one of the main features in cognitive models for 'normal' Obsessive-Compulsive Disorder , 2008). The relationship between responsibility attitudes and OC symptoms has been well studied ., 2008). For example, it was found that manipulation of responsibility among patients with OCD triggered new symptoms (Arntz, Voncken, & Goosen, 2007). It can therefore be stated that the role of responsibility is established in OC symptoms ., 2008).
However, assumptions about a role of impulsiveness in OCD grow in number. According to the DSM-IV, impulse control disorders are characterized by 'the failure to resist an impulse, drive or temptation to perform an act that is harmful to the person or others' (American Psychiatric Association, 2000) (den Heuvel et al., 2010). It is possible that there is a connection between compulsive and impulsive disorders. In that case, the relationship between compulsivity (including excessive responsibility) and impulsiveness accounts for OC symptoms ., 2008).

According to this view, it is more logical to refer to the Obsessive-Compulsive Spectrum Disorder (OCSD) (Hollander, 2005). OCSD can be separated in three distinct clusters, characterizing either one of them by body appearance, impulsiveness or neurological based disorders, *see table 2* (Hollander, 2005).
OCD and OCSD have many similarities, but share one core feature; obsessive thinking and compulsive behaviours, specifically characterizing OCD, can be found in OCSD as well. However, whereas patients suffering from OCD usually have good insight in their disorder, meaning that they recognize the craziness of the thoughts and compulsions, but simply cannot resist, patients suffering from OCSD usually have poor insight (Hollander, 2005).

Another shared feature is that of co-morbidity. OCD patients often have OCSD symptoms during the course of the illness. Besides, it is shown that in family members of OCD patients, disorders that fall in one the categories of OCSD are more prevalent. This could indicate a genetic component coding for core symptoms across different conditions (Hollander, 2005).

Table 2: Distinct clusters identified in OCSD (Hollander, 2005)

Cluster 1	Cluster 2	Cluster 3
***Obsessed with issues concerning bodily sensations, body appearance or body weight** ***Body dysmorphic disorder, anorexia nervosa**	***'Impulsive disorders'. Impulses are followed and then pleasure, arousal or stimulation is experienced. Guilt or remorse is felt afterwards** ***Sexual compulsions, hair pulling, pathological gambling, self-injurious behavior, kleptomania**	***Neurologically based disorders, affecting the basal ganglia** ***Tourette's syndrome, autism**

The whole concept of an OCD spectrum can be moved towards terms of compulsivity and impulsivity (Hollander, 2005) (Lochner & Stein, 2006) (Ravindran, Da Silva, Ravindran, Richter, & Rector, 2009), *see table 3*. At the compulsive end of the spectrum OCD is present, comprising a disorder in which patients show risk aversive, harm avoidant behaviour. They perform rituals to neutralize anxiety or threat. At the impulsive end of the spectrum individuals are found who perform risky behaviour and underestimate harm, of which pathological gambling is an example (Hollander, 2005) (Lochner & Stein, 2006). In the middle of the spectrum, conditions are found that comprise both compulsive and impulsive features, for example autism (Hollander, 2005) (Lochner & Stein, 2006).

Table 3: The compulsive-impulsive spectrum in which disorders are divided based on the features present (Hollander, 2005)

Compulsivity	Obsessive-Compulsive Disorder
	Body Dysmorphic Disorder
	Anorexia Nervosa
	Depersonalisation
	Hypochondriasis
	Tourette's Syndrome
	Trichotillomania
	Autism
	Binge eating
	Compulsive buying
	Kleptomania
	Pathological Gambling
	Self-injurious Behaviour
	Sexual Compulsions
	Borderline Personality Disorder
Impulsivity	Anti-social Personality Disorder

It has been made clear why compulsivity (harm avoidant) and impulsivity (reward seeking) should be seen as distinct features, both with comprising their own disorders. However, the conditions 'compulsivity' and 'impulsivity' are often mixed. Such an intermixing of terms increases the difficulty in the discussion on the differences and similarities between the symptoms found in the (OCD) spectrum (den Heuvel et al., 2010).

Another argument for dividing compulsivity and impulsivity is the pathophysiology. It is suggested that impulsivity is associated with a deficiency in orbito-frontal activity, whereas compulsivity is connected to an hyperactive orbito-frontal region (Hollander, 2005). However, neuro-anatomical models put forward the existence of separate, but intercommunicating circuits (Fineberg et al., 2010). One model examines the compulsive and impulsive cortico-striatal circuits. The compulsive circuit, which has been discussed before, is driven by a striatal component (caudate nucleus) and the inhibitory control over the compulsive behaviour is regulated by the OFC (prefrontal component). Similarly, the impulsive circuit is driven by the ventral striatum / NAcc (striatal component) and the inhibitory control over the impulsive behaviour is exerted by the prefrontal component (anterior cingulate / ventromedial PFC) (Fineberg et al., 2010). In other words, if this model is correct, compulsive and impulsive behaviours are driven by striatal neural

circuits and inhibited by prefrontal circuits. Thus, hyperactivity in any striatal component or hypoactivity in any prefrontal component may then result in an elevated propensity for executing either impulsive or compulsive behaviour (Fineberg et al., 2010).
To summarize, compulsive and impulsive disorders are traditionally seen as opposite ends of the spectrum. Nevertheless, increasing evidence suggests a shared tendency toward behavioural disinhibition; either a failure in cortical control over striatal circuits or an overactivity in the striatal circuits itself (Fineberg et al., 2010).

Impulsivity and compulsivity can also be subdivided according to neurocognitive domains (Fineberg et al., 2010). Impulsivity can then be divided in motor impulsivity ('motor disinhibition'), decision-making impulsivity ('choosing a small immediate reward over a larger delayed reward despite negative long-term consequences') and reflection impulsivity ('insufficient information sampling before making a choice'). Compulsivity can be seen as cognitive inflexibility, divided in reversal learning ('inability to adapt behaviour after negative feedback') and attentional set-shifting ('inability to switch attention between stimuli') (Fineberg et al., 2010). These forms of cognitive inflexibility seem to act through distinct brain areas (OFC versus ventrolateral PFC) and are influenced by different neurotransmitter systems (serotonin versus dopamine) (Fineberg et al., 2010).
Neurocognitive domains can thus provide a separation of distinct impulsive and compulsive features, based on the definition, neural systems and neurochemistry. Also, different tasks and animal models have been developed and match to each neurocognitive domain; these will be explained in *the next paragraph* (Fineberg et al., 2010).

3.2 Serotonin and dopamine differences in animal models for impulsive and compulsive behaviour

Considering serotonin in relation to impulsive and compulsive behaviour, intriguing differences have been observed. As mentioned in *chapter 2*, the 5-HT_{2A} and 5-HT_{2C} receptors seem to play a crucial role in compulsivity. In an animal model for choices and reaction time (Robbins, 2002), administration of a 5-HT_{2C} receptor antagonist worsened the impulsivity observed. In contrast, administration of a 5-HT_{2A} receptor antagonist had a different action; reduced impulsivity was seen (Fineberg et al., 2010). Making the matter even more complex, these antagonists had opposite effects on compulsivity. Another animal model, considering reversal learning, showed that 5-HT_{2C} receptor antagonism facilitated this form of cognitive inflexibility. The 5-HT_{2A} receptor antagonist impaired reversal learning. These findings are combined in *table 4* (Fineberg et al., 2010). Besides animal models, studies in OCD patients show both impulsive and compulsive features, as depicted by poor performance on several human tasks. In this case, it was also shown that unaffected first-degree relatives of patients have an alike impairment on such tasks, thus, despite a lack of symptoms, exhibiting similar levels of motor impulsivity and cognitive inflexibility (Fineberg et al., 2010).

Table 4: Effects of 5-HT_{2A} and 5-HT_{2C} receptor antagonists on animal models for compulsivity and impulsivity (Fineberg et al., 2010)

	Compulsivity	**Impulsivity**
5-HT_{2A} receptor antagonist	Reduced	Increased
5-HT_{2C} receptor antagonist	Increased	Reduced
Hypothesized pathophysiology	OFC to caudate nucleus	Ventromedial PFC to NAcc

Considering dopamine, it has been mentioned before that this neurotransmitter has a important role in reward (Fineberg et al., 2010). It is hypothesized that stimulation of the mesolimbic dopamine pathway sensitizes the reward system and leads to an increase in reward seeking. This might facilitate impulsive-motivated behaviours, which are dopamine related. Keeping in mind that substance abusers have a decreased activity of the mesolimbic and mesocortical dopamine systems, this might cause a 'compulsion' to look for stronger rewards; the dopamine deficiency needs to be replenished (Fineberg et al., 2010). In this way, the aforementioned hypothesis of a dysregulated dopamine

system after repeated stimulation of dopamine release (for example via drugs) seems to be confirmed. Basically, the increased dopamine release leads to enhanced reward seeking due to a compulsive drive towards restoring a dopamine deficiency, by means of reward stimulation (Fineberg et al., 2010).

An animal model to study impulsivity is the 'delay discounting task' (Zeeb, Floresco, & Winstanley, 2010). As mentioned before, impulsiveness is accompanied by a preference for smaller immediate rewards, instead of the larger delayed rewards. This is seen as a 'intolerance to delay-of-gratification'. The OFC seems to play an important role in this impulsive choice and also dopamine is influenced. It is thought that dopaminergic innervations of the OFC have a role in mediating 'delay discounting judgements'; microdialysis studies indicate that dopamine turnover in the OFC is enhanced when animals are performing these judgements (Zeeb et al., 2010).
Amphetamine is believed to decrease impulsive decision making in the model for delay discounting (Winstanley, Theobald, Dalley, & Robbins, 2005). On the contrary, dopamine antagonists increases impulsive decision making. Within the medial prefrontal cortex, decreasing dopaminergic activity at D_1 receptors increases impulsive choice, although the exact roles of D_1 and D_2 receptors are still unclear (Zeeb et al., 2010).

Another animal model, the five-choice serial reaction time task paradigm (5-CSRTT), mentioned above as 'an animal model for choices and reaction time', is used as a reflection of impulsivity in rats (Puumala & Sirviö, 1998). Both dopamine and serotonin can have an influence on this task, as suggested in a study measuring both the concentrations of these neurotransmitters as well as their metabolites. It was found that changes in dopamine and serotonin turnover in the frontal cortex account for impulsivity in rats (Puumala & Sirviö, 1998). As stated in another animal study (Eagle et al., 2009), generalized depletion of serotonin in the brain disrupts certain aspects of impulsive action. It can therefore be implicated that serotonin modulates a concept of behavioural inhibition that controls impulsive responding (Eagle et al., 2009).

Finally, the nucleus accumbens is suggested to play an important role in impulsivity (Besson et al., 2010) (Winstanley et al., 2005). Serotonin and dopamine (interactions) within the NAcc are prominent in the control of impulsivity (Winstanley et al., 2005). A dopamine $D_{2/3}$ receptor antagonist (nafadotride) increased the level of impulsivity when infused into the NAcc shell, but decreased impulsivity when infused into the NAcc core (Besson et al., 2010). A dopamine $D_{2/3}$ receptor partial agonist (aripiprazole) decreased impulsive behaviour when administered systemically, but had no effect when infused in either shell or core (Besson et al., 2010). Besides, it is known that 5-HT_{1A} receptors are

located on dopaminergic cells in the part of the ventral tegmental area (VTA) that projects to the NAcc and also they are found within the NAcc itself (Winstanley et al., 2005). This all might implicate a role for both neurotransmitters simultaneously on the course of an impulsive action and, as mentioned earlier in this paragraph and the previous chapter, also for compulsivity.

Chapter 4: Future directions

4.1 Serotonin and dopamine: 'the new pathway' (including neuropeptides and noradrenaline)

The data described in *chapter 2* shows that it is not yet fully understood how dopamine and serotonin interact. Is it via 5-HT_{2A} and 5-HT_{2C} receptor antagonism, is there a role for glutamate or is the imbalance between direct and indirect pathways in the basal ganglia 'the way to go'? Over time, new insights will reveal what the real mechanisms of action for SSRI's and antipsychotics are. Until that time, speculating about the interaction, based on the observed effect of treatment and imaging studies, is all that is left. Besides speculating about the interaction of serotonin and dopamine only, other factors also might be involved. Neuropeptides like arginine vasopressin, oxytocin and somatostatin are also possible to play a role in OCD (Zohar, Chopra, Sasson, Amiaz, & Amital, 2000). To pick one example, it was found that cerebrospinal fluid levels of oxytocin were elevated in OCD patients compared to healthy controls (Leckman et al., 1994). It was even the case of severity of symptoms being correlated to the raised oxytocin level in the fluid (Leckman et al., 1994). Also noradrenaline has been implicated in the disorder. In a meta-study, it was shown that the SNRI (serotonin noradrenaline reuptake inhibitor) venlafaxine was as effective as the SSRI paroxetine and well-tolerated by patients (Dell'Osso, Nestadt, Allen, & Hollander, 2006). Although not to be considered as a first line of treatment, it seems to act as a good alternative for treatment resistant patients. Particularly at a higher dose range, venlafaxine seems to be effective in OCD sufferers (Dell'Osso et al., 2006). The mechanisms of action of an SNRI is the same as that of a SSRI, including blockage of the reuptake of noradrenaline and therefore increasing the availability of this neurotransmitter in the synaptic cleft (Dell'Osso, Buoli, Baldwin, & Altamura, 2010).

Taken altogether, to examine the peripheral markers of, for example, serotonergic functioning, blood studies and cerebrospinal fluid studies can be conducted (Zohar et al., 2000). The levels of serotonin and its metabolite 5-HIAA can be measured to give an indication on the difference between non-medicated and medicated patients, regarding serotonin function (Zohar et al., 2000). Pharmacological challenge studies and treatment response studies can also be of worth to observe the action mechanisms of the neurotransmitters involved (Zohar et al., 2000) (Markarian et al., 2010). Via these studies, new pathways can be proposed and examined. Although the hyperactivity in the cortico-striato-thalamocortical pathway will be of main interest for future studies, it is possible that other structures are also involved.

In conclusion, obsessive-compulsive disorder seems to result from a disruption in information processing within the loops connecting the prefrontal cortex to the basal ganglia (Aouizerate, Guehl et al., 2004). However, it is still unclear what the exact roles of serotonin and dopamine are in this theory. Besides, glutamate can turn out to be the neurotransmitter mostly overlooked, but very important. Several models have been proposed; the 'Modell', 'Baxter' and 'Schwartz' models, each of which underlining a particular aspect of disruption in information processing (Aouizerate, Guehl et al., 2004). Thus, so far it can be concluded that the basics (anatomical pathways) underlying OC symptoms are known, now the details (neurotransmitter pathways) have to be studied and fill in the remaining gaps.

4.2 Compulsive and impulsive behaviour: 'both present in OCD'

A relative new suggestion is the implication that impulsivity drives compulsivity. The question addresses whether is it possible to show (pathological) compulsivity without motor impulsivity (Fineberg et al., 2010). It could also be the case that over time impulsive habits, as in pathological gambling, shift toward a more compulsive pattern of behaviour (Fineberg et al., 2010). But this is mere speculating; no data has yet proved this suggestion.

To summarize, the compulsive end of the spectrum, characterized by 'over-control' and behavioural inhibition, is linked to increased serotonergic and frontal activity, whereas the impulsive end of the spectrum, characterized by deficient control and behavioural disinhibition, is linked to decreased serotonergic and frontal function (Lochner & Stein, 2006). Although the distinction might be clear, some patients with OCD score high on both compulsivity and impulsivity ratings, which makes a complete opposition of both features impossible. This means that instead of a one-dimensional approach, it might be better to look at the obsessive-compulsive spectrum in a multi-dimensional way; different dimensions can be complementary (Lochner & Stein, 2006).

4.3 Animal models for OCD can contribute to validating serotonin and dopamine (inter)action in compulsive and impulsive behaviour

As shown before, animal models are very important in gaining more insight in OCD. Due to the increasing number of animal models developed by researchers, treatments are carefully being examined. Besides, more knowledge is provided about how exactly these treatments have their mechanism of action. An animal model not mentioned before, but worth to be brought up, is the scheduled-induced polydipsia (Woods et al., 1993) (van Kuyck, Brak, Das, Rizopoulos, & Nuttin, 2008). Food deprived rats that are exposed to a procedure in which food is delivered once in a while, will drink large amounts of water when the opportunity is there to do so. This is an example of adjunctive behaviours and these are proposed as animal models for human compulsions. Excessive behaviour is also seen in patients, hence the animal model of schedule-induced polydipsia for OCD (Woods et al., 1993) (van Kuyck et al., 2008).

Genetic models include the mouse Hoxb8 mutant that results in excessive grooming, leading to hair removal and lesions (Greer & Capecchi, 2002). This behaviour resembles that of a type of OCD, trichotillomania, with aberrant hair pulling as the main characteristic (Greer & Capecchi, 2002). Besides, Hoxb8 is expressed in the 'OCD-region' of the brain, therefore establishing a link between this transcription factor and OCD (Greer & Capecchi, 2002). Another genetic model is that of the dopamine transporter gene knockdown in mice (Berridge, Aldridge, Houchard, & Zhuang, 2005). This leads to a rise (170%) of the extracellular dopamine levels in the neostriatum of the mutant mice, resulting in stronger and more rigid grooming chain patterns (Berridge et al., 2005).

Besides these laboratory models (genetic, pharmacological and behavioural), several ethological models are also present for OCD in animals (Boulougouris et al., 2009). In these models, animals have spontaneous persistent behaviours with genetic components reminiscent of OCD (Boulougouris et al., 2009). However, practicality is low (Boulougouris et al., 2009). Examples of ethological models include tail-chasing in the dog (Boulougouris et al., 2009) (Brown, Crowell-Davis, Malcolm, & Edwards, 1987), hair pulling in cats (Boulougouris et al., 2009) (Swanepoel, Lee, & Stein, 1998), feather picking in birds (Boulougouris et al., 2009) (Grindlinger & Ramsay, 1991) and cribbing in horses (Boulougouris et al., 2009) (Luescher, McKeown, & Dean, 1998).

4.4 Conclusions on the future directions: implications of the previous findings and suggestions for treatment

Although a substantial number of patients with OCD do not respond to SSRI's, it still is the first line of treatment, besides behavioural therapy. Adjuvant medication of antipsychotics also have shown beneficial effects in treatment-resistant patients and as mentioned before, SNRI's work as well as SSRI's. So what does this all mean? Is serotonin the main neurotransmitter to focus upon, or are the more current studies right and is there more to it? But is it logical to assume that OCD is only present because of a dysfunction of serotonin, dopamine, noradrenaline, opioids, steroids, oxytocin and vasopressin (Lochner & Stein, 2006)? And then there is also the idea that OCD may be mediated by the immune system (Lochner & Stein, 2006). Is this not all too much? Any researcher can find a patient with OCD and link it to the system of choice, but does this mean that the majority of patients has a complete failed neurotransmitter/neuropeptide system? It is illogical to assume that OCD is a consequence of only learning principles and perhaps bad parenting or neglect in the childhood. Genetic studies show that a family history of OCD is relatively common (Aouizerate, Guehl et al., 2004). Also, twin studies suggest that genetic factors play an important role in the appearance of OCD (Aouizerate, Guehl et al., 2004). But the question remains: to what degree do all of these systems interact in the expression of OCD? A drug related to serotonin receptors (especially 5-HT_{2A} and 5-HT_{2C}) will always have some effect on animals or patients, but is this not also the case for healthy subjects, since there is, after all, interference with a very important neurotransmitter system (Davidson & Bjorgvinsson, 2003). The only way to find out is to test all these drugs not only in patients or animals expressing compulsive-like behaviour, but also in healthy controls.

Besides, it can be stated that it is very complicated to develop an animal model in which both dopamine and serotonin theories can be tested. It is either one or the other up to date, but a suggestion could be made towards finding an animal model in which both serotonin and dopamine challenges can be evaluated.

To make matters even more complicated, there also is the presence of a compulsive-impulsive spectrum. OCD patients are divided into the very compulsive end of the spectrum, but as discussed in the previous parts, they can also exhibit impulsive features. However, the impulsive features are associated with a different malfunctioning of the, for example, serotonergic and frontal systems than compulsive features (Lochner & Stein, 2006).

How does all of this then result in suggestions for 'the new treatment'? It does not. It will be impossible to find one treatment that suits every patient. Therefore, the only suggestions to be made are more research on obsessive, compulsive and impulsive features. This can be conducted via animal models covering compulsive and/or impulsive aspects, but also in clinical trials with patients receiving different types of approved medication. Medication that does not have to be designed especially for OCD, but, like antipsychotics, have an effect found by accident. And then the most important suggestion: to treat every patient as a person and not as a number. An OCD patient is also helped by attention and support. Treatment has to be evaluated individually and a plan has to be set up to find the most favourable type of drug and dose. Only then, OCD patients can be treated in an optimal way and this is perhaps the most important goal of all research combined: improving the quality of life.

References

Alevizos, B., Lykouras, L., Zervas, I. M., & Christodoulou, G. N. (2002). Risperidone-induced obsessive-compulsive symptoms: A series of six cases. *Journal of Clinical Psychopharmacology, 22*(5), 461-467. Retrieved from SCOPUS database.

American Psychiatric Association. (2000). *Diagnostic and statistical manual of mental disorders. 4th edition, text revision (DSM-IV-TR)*. *Washington, DC: American Psychiatric Association,*

American Psychiatric Association. (July 2007). [Guideline] american psychiatric association work group on obsessive-compulsive disorder. practice guideline for the treatment of patients with obsessive-compulsive disorder. *Am J Psychiatry, 164(suppl)*, 1-56.

Aouizerate, B., Cuny, E., Martin-Guehl, C., Guehl, D., Amieva, H., Benazzouz, A., et al. (2004). Deep brain stimulation of the ventral caudate nucleus in the treatment of obsessive-compulsive disorder and major depression: Case report. *Journal of Neurosurgery, 101*(4), 682-686. doi:10.3171/jns.2004.101.4.0682

Aouizerate, B., Guehl, D., Cuny, E., Rougier, A., Bioulac, B., Tignol, J., et al. (2004). Pathophysiology of obsessive-compulsive disorder: A necessary link between phenomenology, neuropsychology, imagery and physiology. *Progress in Neurobiology, 72*(3), 195-221. Retrieved from SCOPUS database.

Arntz, A., Voncken, M., & Goosen, A. C. A. (2007). Responsibility and obsessive-compulsive disorder: An experimental test. *Behaviour Research and Therapy, 45*(3), 425-435. Retrieved from SCOPUS database.

Bergqvist, P. B. F., Dong, J., & Blier, P. (1999). Effect of atypical antipsychotic drugs on 5-HT2 receptors in the rat orbito-frontal cortex: An in vivo electrophysiological study. *Psychopharmacology, 143*(1), 89-96. Retrieved from SCOPUS database.

Berridge, K. C., Aldridge, J. W., Houchard, K. R., & Zhuang, X. (2005). Sequential super-stereotypy of an instinctive fixed action pattern in hyper-dopaminergic mutant mice: A model of obsessive compulsive disorder and tourette's. *BMC Biol, 3*, 4.

Besson, M., Belin, D., McNamara, R., Theobald, D. E. H., Castel, A., Beckett, V. L., et al. (2010). Dissociable control of impulsivity in rats by dopamine D2/3 receptors in the core and shell subregions of the nucleus accumbens. *Neuropsychopharmacology, 35*(2), 560-569. Retrieved from SCOPUS database.

Björgvinsson, T., Hart, J., & Heffelfinger, S. (2007). Obsessive-compulsive disorder: Update on assessment and treatment. *Journal of Psychiatric Practice, 13*(6), 362-372. doi:10.1097/01.pra.0000300122.76322.ad

Blier, P., Habib, R., & Flament, M. F. (2006). Pharmacotherapies in the management of obsessive-compulsive disorder. *Canadian Journal of Psychiatry, 51*(7), 417-430. Retrieved from SCOPUS database.

Boulougouris, V., Chamberlain, S. R., & Robbins, T. W. (2009). Cross-species models of OCD spectrum disorders. *Psychiatry Research, 170*(1), 15-21. doi:10.1016/j.psychres.2008.07.016

Brown, S. A., Crowell-Davis, S., Malcolm, T., & Edwards, P. (1987). Naloxone-responsive compulsive tail chasing in a dog. *J Am Vet Med Assoc, 190*(7), 884-6.

Campbell, K. M., De Lecea, L., Severynse, D. M., Caron, M. G., McGrath, M. J., Sparber, S. B., et al. (1999). OCD-like behaviors caused by a neuropotentiating transgene targeted to cortical and limbic D1+ neurons. *Journal of Neuroscience, 19*(12), 5044-5053. Retrieved from SCOPUS database.

Choi, Y. -. (2009). Efficacy of treatments for patients with obsessive-compulsive disorder: A systematic review. *Journal of the American Academy of Nurse Practitioners, 21*(4), 207-213. doi:10.1111/j.1745-7599.2009.00408.x

Chou-Green, J. M., Holscher, T. D., Dallman, M. F., & Akana, S. F. (2003). Compulsive behavior in the 5-HT2C receptor knockout mouse. *Physiol Behav, 78*(4-5), 641-9.

Davidson, J., & Bjorgvinsson, T. (2003). Current and potential pharmacological treatments for obsessive-compulsive disorder. *Expert Opinion on Investigational Drugs, 12*(6), 993-1001. Retrieved from SCOPUS database.

Dell'Osso, B., Buoli, M., Baldwin, D. S., & Altamura, A. C. (2010). Serotonin norepinephrine reuptake inhibitors (SNRIs) in anxiety disorders: A comprehensive review of their clinical efficacy. *Human Psychopharmacology, 25*(1), 17-29. Retrieved from SCOPUS database.

Dell'Osso, B., Nestadt, G., Allen, A., & Hollander, E. (2006). Serotonin-norepinephrine reuptake inhibitors in the treatment of obsessive-compulsive disorder: A critical review. *Journal of Clinical Psychiatry, 67*(4), 600-610. Retrieved from SCOPUS database.

den Heuvel, O. A. v., der Werf, Y. D. v., Verhoef, K. M. W., de Wit, S., Berendse, H. W., Wolters, E. C., et al. (2010). Frontal-striatal abnormalities underlying behaviours in the compulsive-impulsive spectrum. *Journal of the Neurological Sciences, 289*(1-2), 55-59. Retrieved from SCOPUS database.

Denys, D., Klompmakers, A. A., & Westenberg, H. G. M. (2004). Synergistic dopamine increase in the rat prefrontal cortex with the combination of quetiapine and fluvoxamine. *Psychopharmacology, 176*(2), 195-203. doi:10.1007/s00213-004-1880-0

Denys, D., Van Der Wee, N., Janssen, J., De Geus, F., & Westenberg, H. G. M. (2004). Low level of dopaminergic D2 receptor binding in obsessive-compulsive disorder. *Biological Psychiatry, 55*(10), 1041-1045. Retrieved from SCOPUS database.

Denys, D., Zohar, J., & Westenberg, H. G. M. (2004). The role of dopamine in obsessive-compulsive disorder: Preclinical and clinical evidence. *Journal of Clinical Psychiatry, 65*(SUPPL. 14), 11-17. Retrieved from SCOPUS database.

Dougherty, D. D., Rauch, S. L., & Jenike, M. A. (2004). Pharmacotherapy for obsessive-compulsive disorder. *Journal of Clinical Psychology, 60*(11), 1195-1202. Retrieved from SCOPUS database.

Eagle, D. M., Lehmann, O., Theobald, D. E. H., Pena, Y., Zakaria, R., Ghosh, R., et al. (2009). Serotonin depletion impairs waiting but not stop-signal reaction time in rats: Implications for theories of the role of 5-HT in behavioral inhibition. *Neuropsychopharmacology, 34*(5), 1311-1321. doi:10.1038/npp.2008.202

El Mansari, M., & Blier, P. (2006). Mechanisms of action of current and potential pharmacotherapies of obsessive-compulsive disorder. *Progress in Neuro-Psychopharmacology and Biological Psychiatry, 30*(3), 362-373. Retrieved from SCOPUS database.

El Mansari, M., Bouchard, C., & Blier, P. (1995). Alteration of serotonin release in the guinea pig orbito-frontal cortex by selective serotonin reuptake inhibitors. relevance to treatment of obsessive-compulsive disorder. *Neuropsychopharmacology, 13*(2), 117-127. Retrieved from SCOPUS database.

emedicine. (2010). *Http://emedicine.medscape.com/article/287681-overview*. Retrieved June, 2010, from

Fineberg, N. A., Potenza, M. N., Chamberlain, S. R., Berlin, H. A., Menzies, L., Bechara, A., et al. (2010). Probing compulsive and impulsive behaviors, from animal models to endophenotypes: A narrative review. *Neuropsychopharmacology, 35*(3), 591-604. Retrieved from SCOPUS database.

Goddard, A. W., Shekhar, A., Whiteman, A. F., & McDougle, C. J. (2008). Serotoninergic mechanisms in the treatment of obsessive-compulsive disorder. *Drug Discovery Today, 13*(7-8), 325-332. Retrieved from SCOPUS database.

Goodman, W. K., Barr, L. C., McDougle, C. J., & Price, L. H. (1993). Beyond the serotonin hypothesis of OCD. *European Neuropsychopharmacology, 3*(3), 229. Retrieved from SCOPUS database.

Goodman, W. K., Price, L. H., Rasmussen, S. A., Mazure, C., Delgado, P., Heninger, G. R., et al. (1989). The yale-brown obsessive compulsive scale. II. validity. *Archives of General Psychiatry, 46*(11), 1012-1016. Retrieved from SCOPUS database.

Goodman, W. K., Price, L. H., Rasmussen, S. A., Mazure, C., Fleischmann, R. L., Hill, C. L., et al. (1989). The yale-brown obsessive compulsive scale. I. development, use and reliability. *Archives of General Psychiatry, 46*(11), 1006-1011. Retrieved from SCOPUS database.

Greer, J. M., & Capecchi, M. R. (2002). Hoxb8 is required for normal grooming behavior in mice. *Neuron, 33*(1), 23-34.

Grindlinger, H. M., & Ramsay, E. (1991). Compulsive feather picking in birds. *Arch Gen Psychiatry, 48*(9), 857.

Hollander, E. (2005). Obsessive-compulsive disorder and spectrum across the life span. *International Journal of Psychiatry in Clinical Practice, 9*(2), 79-86. Retrieved from SCOPUS database.

Jackson, C. W., Morton, W. A., & Lydiard, R. B. (1994). Pharmacologic management of obsessive-compulsive disorder. *Southern Medical Journal, 87*(3), 310-321. Retrieved from SCOPUS database.

Joel, D., & Avisar, A. (2001). Excessive lever pressing following post-training signal attenuation in rats: A possible animal model of obsessive compulsive disorder? *Behavioural Brain Research, 123*(1), 77-87. Retrieved from SCOPUS database.

Joel, D., & Doljansky, J. (2003). Selective alleviation of compulsive lever-pressing in rats by D1, but not D2, blockade: Possible implications for the involvement of D1 receptors in obsessive-compulsive disorder. *Neuropsychopharmacology : Official Publication of the American College of Neuropsychopharmacology, 28*(1), 77-85. Retrieved from SCOPUS database.

Joel, D., Doljansky, J., Roz, N., & Rehavi, M. (2005). Role of the orbital cortex and of the serotonergic system in a rat model of obsessive compulsive disorder. *Neuroscience, 130*(1), 25-36. Retrieved from SCOPUS database.

Joel, D., Doljansky, J., & Schiller, D. (2005). 'Compulsive' lever pressing in rats is enhanced following lesions to the orbital cortex, but not to the basolateral nucleus of the amygdala or to the dorsal medial prefrontal cortex. *European Journal of Neuroscience, 21*(8), 2252-2262. Retrieved from SCOPUS database.

Katz, R. J. (1991). Neurobiology of obsessive compulsive disorder - A serotonergic basis of freudian repression. *Neuroscience and Biobehavioral Reviews, 15*(3), 375-381. Retrieved from SCOPUS database.

Kopell, B. H., Greenberg, B., & Rezai, A. R. (2004). Deep brain stimulation for psychiatric disorders. *Journal of Clinical Neurophysiology, 21*(1), 51-67. doi:10.1097/00004691-200401000-00007

Leckman, J. F., Goodman, W. K., North, W. G., Chappell, P. B., Price, L. H., Pauls, D. L., et al. (1994). Elevated cerebrospinal fluid levels of oxytocin in obsessive-compulsive disorder: Comparison with tourette's syndrome and healthy controls. *Archives of General Psychiatry, 51*(10), 782-792. Retrieved from SCOPUS database.

Lochner, C., & Stein, D. J. (2006). Does work on obsessive-compulsive spectrum disorders contribute to understanding the heterogeneity of obsessive-compulsive disorder? *Progress in Neuro-Psychopharmacology and Biological Psychiatry, 30*(3), 353-361. Retrieved from SCOPUS database.

Luescher, U. A., McKeown, D. B., & Dean, H. (1998). A cross-sectional study on compulsive behaviour (stable vices) in horses. *Equine Vet J Suppl,* (27), 14-8.

Markarian, Y., Larson, M. J., Aldea, M. A., Baldwin, S. A., Good, D., Berkeljon, A., et al. (2010). Multiple pathways to functional impairment in obsessive-compulsive disorder. *Clinical Psychology Review, 30*(1), 78-88. Retrieved from SCOPUS database.

Math, S. B., & Janardhan Reddy, Y. C. (2007). Issues in the pharmacological treatment of obsessive-compulsive disorder. *International Journal of Clinical Practice, 61*(7), 1188-1197. doi:10.1111/j.1742-1241.2007.01356.x

Matsunaga, H., Nagata, T., Hayashida, K., Ohya, K., Kiriike, N., & Stein, D. J. (2009). A long-term trial of the effectiveness and safety of atypical antipsychotic agents in augmenting SSRI-refractory obsessive-compulsive disorder. *Journal of Clinical Psychiatry, 70*(6), 863-868. Retrieved from SCOPUS database.

Meck, W. H. (2006). Neuroanatomical localization of an internal clock: A functional link between mesolimbic, nigrostriatal, and mesocortical dopaminergic systems. *Brain Research, 1109*(1), 93-107. Retrieved from SCOPUS database.

Nuttin, B. J., Gabriëls, L. A., Cosyns, P. R., Meyerson, B. A., Andréewitch, S., Sunaert, S. G., et al. (2008). Long-term electrical capsular stimulation in patients with obsessive-compulsive disorder. *Neurosurgery, 62*(6 SUPPL.) doi:10.1227/01.NEU.0000064565.49299.9A

oknation. (2010). *Http://www.oknation.net/blog/moh-den/2009/09/16/entry-1*. Retrieved June, 2010, from

Olver, J. S., O'Keefe, G., Jones, G. R., Burrows, G. D., Tochon-Danguy, H. J., Ackermann, U., et al. (2009). Dopamine D1 receptor binding in the striatum of patients with obsessive-compulsive disorder. *Journal of Affective Disorders, 114*(1-3), 321-326. Retrieved from SCOPUS database.

Olver, J. S., O'Keefe, G., Jones, G. R., Burrows, G. D., Tochon-Danguy, H. J., Ackermann, U., et al. (2010). Dopamine D1 receptor binding in the anterior cingulate cortex of patients with obsessive-compulsive disorder. *Psychiatry Research - Neuroimaging, 183*(1), 85-88. Retrieved from SCOPUS database.

Phillipson, S. (2010). *Guilt beyond a reasonable doubt.* Retrieved 25th July, 2010, from http://www.ocdonline.com/articlephillipson2.php

Pogarell, O., Poepperl, G., Mulert, C., Hamann, C., Sadowsky, N., Riedel, M., et al. (2005). SERT and DAT availabilities under citalopram treatment in obsessive-compulsive disorder (OCD). *European Neuropsychopharmacology, 15*(5), 521-524. Retrieved from SCOPUS database.

Pum, M., Carey, R. J., Huston, J. P., & Müller, C. P. (2007). Dissociating effects of cocaine and d-amphetamine on dopamine and serotonin in the perirhinal, entorhinal, and prefrontal cortex of freely moving rats. *Psychopharmacology, 193*(3), 375-390. Retrieved from SCOPUS database.

Puumala, T., & Sirviö, J. (1998). Changes in activities of dopamine and serotonin systems in the frontal cortex underlie poor choice accuracy and impulsivity of rats in an attention task. *Neuroscience, 83*(2), 489-499. Retrieved from SCOPUS database.

Ramesh Kumar, T. C., & Khanna, S. (2000). Lamotrigine augmentation of serotonin re-uptake inhibitors in obsessive-compulsive disorder. *Australian and New Zealand Journal of Psychiatry, 34*(3), 527-528. Retrieved from SCOPUS database.

Rauch, S. L., Dougherty, D. D., Malone, D., Rezai, A., Friehs, G., Fischman, A. J., et al. (2006). A functional neuroimaging investigation of deep brain stimulation in patients with obsessive-compulsive disorder. *Journal of Neurosurgery, 104*(4), 558-565. doi:10.3171/jns.2006.104.4.558

Ravindran, A. V., Da Silva, T. L., Ravindran, L. N., Richter, M. A., & Rector, N. A. (2009). Obsessive-compulsive spectrum disorders: A review of the evidence-based

treatments. *Canadian Journal of Psychiatry, 54*(5), 331-343. Retrieved from SCOPUS database.

Robbins, T. W. (2002). The 5-choice serial reaction time task: Behavioural pharmacology and functional neurochemistry. *Psychopharmacology, 163*(3-4), 362-380. Retrieved from SCOPUS database.

Salamone, J. D., Correa, M., Mingote, S. M., & Weber, S. M. (2005). Beyond the reward hypothesis: Alternative functions of nucleus accumbens dopamine. *Current Opinion in Pharmacology, 5*(1), 34-41. Retrieved from SCOPUS database.

Schilman, E. A., Klavir, O., Winter, C., Sohr, R., & Joel, D. (2010). The role of the striatum in compulsive behavior in intact and orbitofrontal-cortex-lesioned rats: Possible involvement of the serotonergic system. *Neuropsychopharmacology, 35*(4), 1026-1039. Retrieved from SCOPUS database.

, S. (2008). Responsibility and impulsivity and their interaction in relation to obsessive-compulsive symptoms. *Journal of Behavior Therapy and Experimental Psychiatry, 39*(3), 228-233. Retrieved from SCOPUS database.

Swanepoel, N., Lee, E., & Stein, D. J. (1998). Psychogenic alopecia in a cat: Response to clomipramine. *J S Afr Vet Assoc, 69*(1), 22.

Szechtman, H., Eckert, M. J., Tse, W. S., Boersma, J. T., Bonura, C. A., McClelland, J. Z., et al. (2001). Compulsive checking behavior of quinpirole-sensitized rats as an animal model of obsessive-compulsive disorder(OCD): Form and control. *BMC Neuroscience [Electronic Resource], 2*(1), 4. Retrieved from SCOPUS database.

Szechtman, H., Sulis, W., & Eilam, D. (1998). Quinpirole induces compulsive checking behavior in rats: A potential animal model of obsessive-compulsive disorder (OCD). *Behavioral Neuroscience, 112*(6), 1475-1485. doi:10.1037/0735-7044.112.6.1475

Thoren, P., Asberg, M., & Bertilsson, L. (1980). Clomipramine treatment of obsessive-compulsive disorder. II. biochemical aspects. *Archives of General Psychiatry, 37*(11), 1289-1294. Retrieved from SCOPUS database.

Tizabi, Y., Louis, V. A., Taylor, C. T., Waxman, D., Culver, K. E., & Szechtman, H. (2002). Effect of nicotine on quinpirole-induced checking behavior in rats: Implications for obsessive-compulsive disorder. *Biological Psychiatry, 51*(2), 164-171. doi:10.1016/S0006-3223(01)01207-0

van Kuyck, K., Brak, K., Das, J., Rizopoulos, D., & Nuttin, B. (2008). Comparative study of the effects of electrical stimulation in the nucleus accumbens, the mediodorsal thalamic nucleus and the bed nucleus of the stria terminalis in rats with schedule-induced polydipsia. *Brain Res, 1201*, 93-9.

Weber, M., Talmon, S., Schulze, I., Boeddinghaus, C., Gross, G., Schoemaker, H., et al. (2009). Running wheel activity is sensitive to acute treatment with selective inhibitors for either serotonin or norepinephrine reuptake. *Psychopharmacology, 203*(4), 753-762. doi:10.1007/s00213-008-1420-4

Winstanley, C. A., Theobald, D. E. H., Dalley, J. W., & Robbins, T. W. (2005). Interactions between serotonin and dopamine in the control of impulsive choice in rats: Therapeutic implications for impulse control disorders. *Neuropsychopharmacology, 30*(4), 669-682. Retrieved from SCOPUS database.

Woods, A., Smith, C., Szewczak, M., Dunn, R. W., Cornfeldt, M., & Corbett, R. (1993). Selective serotonin re-uptake inhibitors decrease schedule-induced polydipsia in rats: A potential model for obsessive compulsive disorder. *Psychopharmacology, 112*(2-3), 195-198. Retrieved from SCOPUS database.

Yin, H. H., & Knowlton, B. J. (2006). The role of the basal ganglia in habit formation. *Nature Reviews Neuroscience, 7*(6), 464-476. Retrieved from SCOPUS database.

Zeeb, F. D., Floresco, S. B., & Winstanley, C. A. (2010). Contributions of the orbitofrontal cortex to impulsive choice: Interactions with basal levels of impulsivity, dopamine signalling, and reward-related cues. *Psychopharmacology,* , 1-12. Retrieved from SCOPUS database.

Zhang, W., Perry, K. W., Wong, D. T., Potts, B. D., Bao, J., Tollefson, G. D., et al. (2000). Synergistic effects of olanzapine and other antipsychotic agents in combination with fluoxetine on norepinephrine and dopamine release in rat prefrontal cortex. *Neuropsychopharmacology, 23*(3), 250-262. doi:10.1016/S0893-133X(00)00119-6

Zohar, J., Chopra, M., Sasson, Y., Amiaz, R., & Amital, D. (2000). Obsessive compulsive disorder: Serotonin and beyond. *The World Journal of Biological Psychiatry : The Official Journal of the World Federation of Societies of Biological Psychiatry, 1*(2), 92-100. Retrieved from SCOPUS database.