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Bc. Karolína Mainerová

Effects of memantine and riluzole on learning deficits in an animal model of obsessive-compulsive disorder induced by 8-OH-DPAT sensitization

Vliv memantinu a riluzolu na učení ve zvířecím modelu obsedantně kompulzivní poruchy vyvolaném sensitizací pomocí 8-OH-DPAT

Diploma thesis

Supervisor: prof. RNDr. Aleš Stuchlík, Ph.D., DSc.

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Prohlášení

Prohlašuji, že jsem závěrečnou práci zpracovala samostatně a že jsem uvedla všechny použité informační zdroje a literaturu. Tato práce ani její podstatná část nebyla předložena k získání jiného nebo stejného akademického titulu.

V Praze,

Podpis

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Abstract

Obsessive-compulsive disorder is a chronic psychiatric disease. It seriously limits the quality of life of patients. Treatment of OCD is not yet fully successful and still many patients are left with debilitating symptoms without functioning medication. Animal models of genetic, behavioral, pharmacological, and optogenetic origins are beneficial in the achievement of new understandings of the disease.

Chronic sensitization of serotonin 1A and 7-receptors with an agonist 8-OH-DPAT ((8-hydroxy-2-(di-propylamino)-tetralin hydrobromide) induces perseverative and compulsive behaviors, which is considered to constitute an animal model of OCD. In this thesis, the 8-OH-DPAT model has been tested in the active place avoidance task on Carousel maze to provide information about the model on learning. Second, this model is used to determine, whether co-administration of memantine or riluzole alleviates the cognitive and learning deficits of this model.

To uncover these effects, an active place avoidance task on a Carousel maze was used. Measured criteria were total distance, entrances to the shock sector, total number of shocks, and median speed after the shock. During habituation, the animals were sensitized to 8-OH-DPAT (with a control group that did not receive 8-OH-DPAT but only saline). In an acquisition, two injections were administered to the animals, one with memantine or riluzole or saline and the other with 8-OH-DPAT or saline. In the habituation, we evaluated the effect of 8-OH-DPAT sensitization. In the acquisition, six groups were evaluated: saline control group (Sensitized/Undrugged/Untreated and Unsensitized/Undrugged/Untreated), 8-OH-DPAT control group (Sensitized/Drugged/Untreated), group that received memantine and then 8-OH-DPAT, group that received riluzole and then 8-OH-DPAT (Sensitized/Drugged/Mem/Ril-Treated), memantine and then saline and group that received riluzole and saline (Sensitized/Undrugged/Mem/Ril-Treated). Both memantine – 8-OH-DPAT and riluzole – 8-OH-DPAT groups (Sensitized/Drugged/Mem/Ril-Treated) showed increased hyperlocomotion and errors than all the other groups. These results indicate that memantine nor riluzole is effective in improving OCD symptoms in the 8-OH-DPAT animal model, it rather makes them more intense.

Keywords: obsessive-compulsive disorder (OCD); behavior, brain, animal models, 8-OH-DPAT, riluzole, memantine, learning, learning deficit, memory

Abstrakt

Obsedantně-kompulzivní porucha je chronické psychiatrické onemocnění. Vážně omezuje a mění kvalitu života. Léčba OCD je v této době založena na kombinaci antidepresiv a psychoterapie, presto spoustu pacientů zůstává bez úspěšné léčby, či s přetrvávajícími symptomy. Zvířecí modely založené na genetické, behaviorální, farmakologické a optogenetické manipulaci jsou úspěšným zdrojem pro výzkum tohoto onemocnění i jeho léčby. Chronická senzitizace serotoninových 1A a 7 - receptorů jejich agonistou 8-OH-DPAT ((8-hydroxy-2-(di-npropylamino)-tetralin hydrobromid) indukuje repetitivní a kompulzivní chování, považované za zvířecí analog symptomů OCD. V této práci byl zjišťován jeho vliv na učení a paměť v kolotočovém bludišti během úkolu aktivního vyhýbání se místu. Dalším cílem této práce bylo zjistit, zda společné podávání memantinu nebo riluzolu s 8-OH-DPAT zmírňuje kognitivní účinky a deficity v učení tohoto modelu. Měřená kritéria byla; celková vzdálenost, počet vstupů do zakázaného sektoru, maximální počet šoků a průměrná rychlost po šoku.

Během habituační fáze byla zvířata sensitizována 8-OH-DPAT (s kontrolní skupinou, která dostávala pouze fyziologický roztok). Při akvizici byly zvířatům podávány dvě injekce, jedna s memantinem nebo riluzolem nebo fyziologickým roztokem a druhá s 8-OH-DPAT nebo fyziologickým roztokem. V habituační fázi jsme vyhodnotili účinek senzitizace 8-OH-DPAT. Při akvizici bylo hodnoceno šest skupin: kontrolní skupina s fyziologickým roztokem (sensitizovaná/bez 8-OH-DPAT/neléčena memantinem a riluzolem a nesensitizovaná/bez 8-OH-DPAT/neošetřená), 8-OH-DPAT kontrolní skupina (senzitizovaná/bez 8-OH-DPAT/neošetřená), skupina, která dostala memantin a poté 8-OH-DPAT, skupina, která dostala riluzole a poté 8-OH-DPAT (senzitizovaná/8-OH-DPAT/Mem/Ril-ošetřená) a skupiny, které dostali memantin nebo riluzole a fyziologický roztok (senzitizovaná/fyziologický roztok/Mem/Ril-ošetřená). Obě skupiny memantin - 8-OH-DPAT a riluzol - 8-OH-DPAT (senzitizovaná/8-OH-DPAT/Mem/Ril-ošetřená) vykazovaly zvýšenou hyperlokomoci a více chyb než všechny ostatní skupiny. Tyto výsledky naznačují, že memantin ani riluzol nejsou účinné při zlepšování symptomů OCD u zvířecího modelu 8-OH-DPAT, spíše je činí intenzivnějšími

Klíčová slova: obsedantně kompulzivní porucha (OCD); chování, mozek, animální modely, 8-OH-DPAT, riluzol, memantin, učení, poruchy učení, paměť

List of abbreviations

The list of abbreviations does not contain abbreviations for genes and proteins.

8-OH-DPAT	8-Hydroxy-2-(Di-n-propylamino) tetralin
AC	Adenylate cyclase
ACC	Anterior cingulate cortex
ACG	Anterior cingulate gyrus
ADHD	Attention deficit hyperactivity disorder
ALS	Amyotrophic lateral sclerosis
AMPA	α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid
ANOVA	Analysis of variance
BG	Basal ganglia
BPD	Borderline personality disorder
BVRT	Benton Visual Retention Test
CANTAB	Cambridge Neuropsychological Test Automated Battery
CBT	Cognitive behavioral therapy
CNF	Cerebrospinal fluid
CNO	Clozapine-N-oxide
CNS	Central nervous system
CSTC	Cortico-striatal-thalamic-cortical
CYBOCS	Children Yale-Brown Obsessive-Compulsive Scale
DA	Dopamine
DBS	Deep brain stimulation
DCS	D-cycloserine
DLPFC	Dorsolateral prefrontal cortex
DOCS	Dimensional obsessive-compulsive scale
DSM	Diagnostic and Statistical Manual of Mental Disorders
EX/RP	Exposure and ritual prevention
fMRI	Functional magnetic resonance
FRIH	Food-restriction induced hyperactivity
GABA	γ-aminobutyric acid
GABHS	Group A beta-hemolytic streptococcal infections
GAD	Generalized anxiety disorder

GPe	Globus pallidus external
GPi	Globus pallidus internal
ICD-11	International classification of disease – 11th edition
ID/ED	Intra-dimensional set-shifting/extra-dimensional set-shifting
INPIOS	Obsessional Intrusive Thoughts Inventory
LED	Light-emitting diode
LSD	Lysergic acid diethylamide
LTP	Long-term potentiation
MB	Mamillary bodies
mCPP	Meta-Chlorophenylpiperazine
MDD	Major depressive disorder
MDMA	3,4-methylendioxymethamfetamin
MRS	Magnetic resonance spectroscopy
MSNs	Medium spiny neurons
MTG	Medial temporal gyrus
NAc	Nucleus accumbens
NAC	N-acetylcystein
NMDA	N-methyl D-Aspartat
NMDAr	N-methyl D-aspartate receptor
OAT	Object alteration task
OCD	Obsessive-compulsive disorder
OFC	Orbitofrontal cortex
OXTR	Oxytocin receptor
PANDAS	Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infection
PET	Positron Emission Tomography
PFC	Prefrontal cortex
PKA	Protein kinase A
PTSD	Post-traumatic stress disorder
RCFT	Rey Osterrieth Complex Figure Test
RM	Repeated measures
ROS	Reactive oxygen species

SERT	Serotonin transporter
SNr	Substantia nigra
SRIs	Serotonin reuptake inhibitors
SSRIs	Selective serotonin reuptake inhibitors
STN	Subthalamic nuclei
TCA	Tricyclic antidepressant
TRAAK	(TWIK Related Arachidonic acid Activated K + channel)
VMS	Ventromedial striatum
VTA	Ventral tegmental area
WAIS-R	Wechsler Adult Intelligence Scale - revisited
WCST	Wisconsin card sorting test
WHO	World health organization
WMS-LM	Wechsler Memory Scale - Logical Memory
YBOCS	Yale-Brown Obsessive-Compulsive Scale

List of contents

1 Introduction

Obsessive-compulsive disorder is a common psychiatric disease with a prevalence of 1-3% (Fontenelle, Mendlowicz, & Versiani, 2006). It is often chronic, heterogeneous and its symptoms can be very time-consuming and debilitating. It is characterized by obsessions - intrusive unwanted thoughts, and compulsions - ritualized behaviors, usually perceived as relieving the anxiety that arises from the obsessions. At present, first-choice and the most effective treatment option for OCD patients are SSRIs at doses higher than in depression and cognitive behavioral therapy (Ninan et al., 2006; Whittal, Thordarson, & Mclean, 2005). This treatment helps approximately 60% of patients, however, some of them still have residual symptoms. Some patients respond well to augmentation SSRIs therapy with atypical antipsychotics (Fineberg, Reghunandanan, Brown, & Pampaloni, 2013). However, for the 40 % of patients that do not respond to SSRIs, novel therapeutic approaches are needed. In line with the involvement of fronto-striatal and frontotemporal connections and neurotransmitter systems involved, agents that alter glutamate transmission could be useful. Since there have been several case studies, that provided good outcomes out of anti-glutamatergic agents (Marinova, Chuang, & Fineberg, 2017; Poyurovsky, Weizman, Weizman, & Koran, 2005; Wu, Hanna, Rosenberg, & Arnold, 2012a), this line of research continues to try to evaluate possible new treatment options in this group of drugs.

In this type of basic and translational research, preclinical animal models are especially useful and effective. Animal models of OCD often depend on their behavioral outcomes, such as hyperactivity, compulsive-like behaviors, and deficits in learning and cognitive functions (Monteiro & Feng, 2016). A 5-HT_{1A} and 5-HT_7 receptor agonist 8-OH-DPAT induces compulsive checking and hyperlocomotion in an open–field arena with objects (Alkhatib, Dvorkin-Gheva, & Szechtman, 2013). In the present study, animals were tested in a Carousel maze in an active place avoidance task, requiring spatial learning and cognitive coordination, to assess learning impairments;

based on the assumption that people with OCD often have problems in cognitive and executive functions and episodic memory (Christensen, Kim, Dysken, & Hoover, 1992; Gillan et al., 2011).

The study aimed to determine, whether riluzole or memantine could alleviate the OCD-related learning deficits in the 8-OH-DPAT animal model. Riluzole is a glutamate transmission modulating agent, that is used for the treatment of amyotrophic lateral sclerosis (ALS). However, it has been prescribed successfully to patients with OCD in off-label trials (Grant, Song, & Swedo, 2010; Pittenger, Krystal, & Coric, 2006). Memantine is a non-competitive NMDA-receptor blocker and is nowadays used for the treatment of dementia and Alzheimer's disease. Its positive effects on cognitive functions suggest that it can be a possible OCD treatment as well (Kishi, Matsuda, & Iwata, 2018b).

2 Review of Literature

2.1 Obsessive-compulsive disorder: an overview

Obsessive-compulsive disorder (OCD) is the fourth most common psychiatric disease. It is often a chronic, heterogeneous, and very debilitating illness. Its prevalence is 1 to 3 % world-widely (Fontenelle et al., 2006), and it is assumed to be the 10th condition most frequently inducing working incapacity (Lopez, 2005). The illness is characterized by reoccurring intrusive thoughts – obsessions and ritualized behaviors that help to release the anxiety that comes from obsessions. These stereotypic actions are called compulsions and even though one usually knows about their futility, they cannot stop doing them. The mechanisms that patients describe are obsessions creating anxiety and compulsions neutralizing this anxiety. However, this cycle is often vastly time-consuming, and it can occupy one's ability to concentrate or even do basic daily activities (Jenike, 2004).

In the ICD-11 (International Classification of Diseases, latest edition 11), OCD is listed under obsessive-compulsive or related disorders. Alongside OCD, in this group are for example body dysmorphophobic disorder, olfactory reference disorder, hypochondriasis, hoarding disorder, trichotillomania, and skin-picking disorder. This classification is established by the WHO (World Health Organization) and is used throughout Europe, the Czech Republic included. It gives each diagnosis alphabetical sign that summarizes a group of diagnoses (Mental and behavioral disorders have an F) and then number code for the specific diagnosis. OCD then has a classification code F.42 6B20 (World Health Organization, 2018). In DSM V (Diagnostic and Statistical Manual of Mental Disorders, latest edition 5) OCD is listed in Obsessive-compulsive and related disorders. This manual is mainly used in the US (American Psychiatric Association, 2013).

There are several diagnostic tools, that were developed to categorize and better understand this heterogeneous disease as well as for the possibility to use more specific treatment. The Yale-Brown Obsessive-Compulsive Scale (Y-BOCS) has scales to determine the severity and presence of various symptoms both in obsessions and compulsions. It divides to 6 groups; 1. obsession about harm due to violence/injury/natural disasters and related compulsions, 2. obsession involving sexual/moral/religious ideas and related compulsions, 3. obsession about symmetry, perception, and compulsion of ordering, sorting, counting, 4. contamination obsession and cleaning compulsions, 5. hoarding obsessions and compulsions, 6. various obsessions and compulsions, such as superstition or physical concern (Mataix-Cols, Rauch, Manzo, Jenike, & Baer, 1999). Y-BOCS is still the most used severity determination tool, however, new measures are being developed, such as the Dimensional Obsessive-Compulsive Scale (DOCS) and the Obsessional Intrusive Thoughts Inventory (INPIOS) (Williams, Mugno, Franklin, & Faber, 2013).

Obsessions can be divided into two categories: autogenous and reactive. Autogenous obsessions come to one's mind without any previous concrete stimuli. In the Y-BOCS scale, categories of taboo, immoral, sexual, and aggressive thoughts, seems to be matching the autogenous spectrum. Those obsessions are usually hard to identify. On the contrary, reactive obsessions come as reaction to actual, more realistic stimuli. Those obsessions are usually easier to identify and tend to create physical compulsions to react to them. Such stimuli are contaminations, mistakes, asymmetry, and loss. People with autogenous obsessions are often threatened by them, or their moral self is being at risk. They often create distractions in the form of compulsions to suppress them. Reactive obsessive patients are on the other hand often convinced, that those stimuli are rational and to be prevented/ceased (Lee & Kwon, 2003).

In a meta-analysis of twenty-one OCD studies, four possible dimensions have been proposed. Those are 1. symmetry obsession with order, repeating, and counting compulsions, 2. taboo thoughts (sexual, religious, aggressive type), 3. obsessions about contamination and cleaning compulsions, and 4. hoarding (Bloch, Landeros-Weisenberger, Rosario, Pittenger, & Leckman, 2008). Interestingly, these dimensions have been linked with different forms of comorbid and pathophysiological conditions. For instance, the early onset of OCD is associated with taboo thoughts and is highly heritable. Taboo thoughts and symmetry/hoarding obsessions are the most familial, genetically conditioned forms of OCD (Hasler et al., 2005). Distinctions in reaction to the medication, therapy, and neural-circuitry patterns can be associated with specific categories of symptoms as well (Mataix-Cols, Marks, Greist, Kobak, & Baer, 2002; Mataix-Cols et al., 2004). I will review different pharmacological treatment options later in this thesis.

OCD onsets sometimes in childhood, though mostly it does in adolescence and early adulthood, with men having earlier onsets than women, and therefore prevalence in childhood patients is greater in men. In the adult population, gender representation is

the same. Earlier onset is predicting sexual/aggressive or symmetry obsessions (Prabhu et al., 2013). Symptoms are usually stable throughout life, however, when they do change, they tend to be in the same category (Williams et al., 2013). Some patients may experience only obsessions without compulsions (more than half of patients with OCD) and vice versa (only about 11 %). Obsessive and compulsive are only 34 % of patients (Torres et al., 2006). Interestingly, many people without OCD diagnosis admit they have gone at some point in their lives through certain obsessive-compulsive states (Ruscio, Stein, Chiu, & Kessler, 2010a).

Comorbidities of other psychiatric conditions are very usual among OCD patients. The most common are major depressive disorder (MDD), generalized anxiety disorder (GAD), and social/specific phobias. There are some differences in early-onset and adult-onset of OCD and gender in terms of comorbidities. Adult-onset OCD often develops on the top of some other mental health problem (Ruscio, Stein, Chiu, & Kessler, 2010b).

2.1.1 Pathophysiology of OCD

Given the heterogeneity of OCD symptoms and comorbidities, a very wide field of probable causes for the illness is on the table. Both biological and environmental factors seem to be important in the etiology of OCD. This was supported by multiple genetic studies, in which 47% of the influence on the onset of OCD is linked to genetic factors and rest to the environment (Van Grootheest, Cath, Beekman & Boomsma, 2005). In the following chapter, I will briefly specify some of the genes related to OCD as well as the most relevant environmental factors that could give rise to OCD onset.

2.1.2 Genes implicated in OCD

Since the 1930s, the heritability of OCD has been proposed. Family studies of OCD indicate that a first degree relative of an OCD patient has 4-10-folds higher risk of

having OCD than in control families. This is much more pronounced in childhood-onset OCD (45-65%) than in adult-onset OCD (27-47%). In twin studies, monozygotic twins had a much higher prevalence of having OCD than dizygotic twins (Van Grootheest et al., 2005). However, OCD is sometimes called “the hidden disease” because many people refuse to seek treatment, either comorbid anxiety and depression being the reasons for such attitude, or not rationally seeing themselves as mentally ill. People with OCD, that do not seek help and therefore do not participate in studies may be producing data bias in those studies (Grabe et al., 2006).

The search for specific genes underlying OCD is still in progress. Supporting the symptom variability, many genes with small effects could be behind the disease. Whole loci including many genes are being studied, mainly for genes coding for transporters, receptors, or enzymes. Nevertheless, there are already some candidate genes with prospective outcomes. They are usually associated with serotonin, dopamine, or glutamate pathways (Shugart et al., 2006; Willour et al., 2004). For instance, the activity of enzyme catechol-O-methyltransferase (COMT) responsible for metabolizing catecholamines, is reduced in OCD patients (Delorme et al., 2010). The most studied COMT polymorphism is a single nucleotide exchange leading to different thermostability (Rutherford, Bennion, Parson, & Daggett, 2006). Subsequently, genes for specific receptor subtypes are broadly studied. SLC1A1 coding for the glutamate transporter EAAT3 (excitatory amino acid transporter 3) with an essential role in the human brain is one of them. It plays an important role in the cortico-striato-thalamo-cortical circuit (CSTC, as reviewed below) and hence supporting the hypotheses that disruption in this circuit is underlying OCD symptomatology (Kanai & Hediger, 2004). SLC1A1 variants are hereditary to male but not female offspring and associated with early-onset but not late-onset OCD. This provides a possible genetic basis for differences in early and late-onset of OCD (Arnold, Sicard, Burroughs, Richter, & Kennedy, 2006). The EAAT1 glutamate transporter coded by SLC1A3 is necessary for the production of important antioxidant glutathione (GSH). Polymorphism in this gene

can cause higher levels of oxidative stress and consequently OCD symptoms (Ersan, Bakir, Erdal Ersan, & Dogan, 2006; Monteiro & Feng, 2016). OCD patients benefit from augmentation to treatment with N-acetyl cysteine (NAC), which is a GSH precursor (Afshar et al., 2012; Paydary et al., 2016).

There are many other genes under examination (serotonergic HTR2A and SLC6A4, dopaminergic DRD3 and DRD4) (Sampaio et al., 2013), however, there are not consistent results that would give promising outcome for the genetic basis of OCD. Rather it looks that many genes with small effects are being somehow disrupted, which leads to initiating this disease, alongside environmental factors acting during the life.

2.1.3 Environmental factors

Regarding environmental factors, there are two common reasons for the outbreak of OCD: stress/trauma and infection. Infection is associated primarily with pediatric patients and it is classified as pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS). When a child is infected with group-A beta-hemolytic streptococcal infections (GABHS) dramatic immune response produces antineuronal antibodies, which can cause autoimmunity reaction with neurons of the basal ganglia and their damage. These children then have tics and motor hyperactivity with many psychiatric comorbidities (Swedo et al., 1998). Sydenham's chorea, neurological response to acute rheumatic fever, which is characterized by discordant behavior and tics (including OCD-spectrum symptoms) is primarily associated with GABHS (Hounie et al., 2004). Mechanisms of neuronal autoimmunity reaction are not clarified yet, nevertheless, there are some research hypotheses. Antibodies for D1 and D2 dopamine receptors could disrupt dopaminergic pathways and change in behavior (Brimberg et al., 2012). Another possible candidate is D8/17 alloantigen found on B lymphocytes and was found elevated in patients with rheumatic fever and tic disorder (Weisz et al., 2004). Other infectious agents can cause similar

symptoms, such as *Mycoplasma pneumoniae* (Müller et al., 2004) or *Borrelia burgdorferi* (Riedel, Straube, Schwarz, Wilske, & Muller, 1998).

2.1.4 Treatment of OCD

OCD patients are often left without treatment for a long time, due to hiding their symptoms or insufficient diagnosis. There are several treatment options; pharmacotherapy (reviewed below), invasive treatment methods such as DBS, or electroconvulsive therapy (Abelson et al., 2005; Greenberg et al., 1997) and psychotherapy. I will briefly review the psychotherapeutic and pharmacologic options in the following sections.

2.1.5 Psychotherapeutic treatment

Nowadays a combination of SSRIs treatment with cognitive-behavioral therapy (CBT) is giving the best outcomes. For OCD patients, specific exposure/ritual prevention (EX/RP) model of CBT has shown great effectiveness. With the help and presence of psychotherapists, the patient is introduced with a particular compulsion creating stimuli. This way the therapist can control and help the patient with learning how to suppress the ritualized responsive behavior (Franklin, Abramowitz, Kozak, Levitt, & Foa, 2000). However, some patients have non-reactive obsessions, or it is extremely hard for them to prevent the compulsion. In those cases, standard individual CBT therapy is comparatively effective (Whittal et al., 2005).

2.1.6 Pharmacological treatment

Modern pharmacologic treatment of OCD began in the 1970-80s with clomipramine, a tricyclic antidepressant (TCA) inhibiting the reuptake of serotonin. Several trials have shown its efficiency in reducing obsessions and compulsions (Jenike et al., 1989; Marks, Mawson, Stern, Cobb, & McDonald, 1980; Mawson, Marks, &

Ramm, 1982). Since expansion in SRIs and SSRIs (e.g., sertraline, fluoxetine, etc.) in last three decades, many patients finally got functioning medication for at least some of their symptoms (Fineberg, Pampaloni, Pallanti, Ipser, & Stein, 2007) and since the SSRIs have fewer significant side-effects than TCAs, they are now the first drug of choice in medicating OCD patients (Bandelow et al., 2008). Higher doses of SSRIs are usually needed for alleviating OCD symptoms than in depression (Ninan et al., 2006). SSRIs effectiveness together with the fact that noradrenergic TCAs such as desipramine were not as effective, supported the importance of serotonin dysfunction in OCD.

However, there are still about 40 % of treatment-resistant patients, or they have residual symptoms. Alongside recognition of other neurotransmitter systems involved in the pathogenesis of OCD (Grados, Atkins, Kovacikova, & McVicar, 2015), new efforts for the use of other than serotonergic agents have progressed (Kellner, 2010). In some cases, augmentation with antipsychotics is applicable (McDougle et al., 1994), as well as memantine (Aboujaoude, Barry, & Gamel, 2009; Poyurovsky et al., 2005) or glycine (Greenberg et al., 2009).

2.2 Neural circuits involved in the psychopathology of OCD

Neurobiology of several psychiatric diseases is still very much obscure, not excluding OCD. However, the basal ganglia circuitry appears to be involved in the pathogenesis of OCD (as well as in other diseases, such as parkinsonism or Huntington's disease). Successful treatment with clomipramine in the late 60s pointed to serotonin circuitry involvement and first steps towards unraveling the basal ganglia (BG) involvement in psychopathology. Later, the knowledge of the BG functioning became greater and other neurotransmitter systems got involved. Structures of these circuits involved in behavioral and affective control are the orbitofrontal, ventromedial, and cingulate cortex, the ventromedial caudate nucleus, the ventral striatum, and the mediodorsal thalamus.

2.2.1 The CSTC loop

In 1983, Penney and Young (Penney & Young, 1983) created a model of the basal ganglia circuitry, in which they proposed, that a positive feedback loop through these structures is behind the beginning, execution, and maintaining of motor behavior. The early characterization of motor control highlighted the importance of the CSTC loop (cortico-striato-thalamic-cortical loop). The CSTC loop is connecting the cortical and subcortical regions of the brain. It contains glutamatergic projections from the orbitofrontal cortex (OFC) to striatum (ventromedial part of the caudate nucleus). This activates inhibitory GABA projections from striatum to the globus pallidus (GP) and substantia nigra (SNr). The direct pathway, creating positive feedback, is driven by releasing inhibitory projections to the thalamus from GPi (globus pallidus interna) and SNr (dopaminergic). The indirect pathway derives from inhibiting GPe (globus pallidus externa), which inhibits the subthalamic nucleus (STN). STN is therefore disinhibited and projects excitatory projections onto the thalamus (ventral anterior and medial dorsal nuclei). The thalamus then closes the loop by exciting back the OFC (Fig.1) (Alexander & Crutcher, 1990). These structures were found to be altered in patients with OCD versus healthy controls, overcharging the direct pathway, hence activating the OFC more and making it more difficult to control motor behavior (Menzies et al., 2008). In PET studies, elevated metabolism in the OFC, the basal ganglia (especially the caudate nucleus), and the thalamus was observed, showing a correlation between metabolism rates and symptom severity and symptom category. People with aggressive obsessions had higher activation of the striatum bilaterally, on the other hand, compulsively cleaning people had the anterior cingulate cortex (ACC), left OFC, and other cortical areas, more active (Saxena & Rauch, 2000).

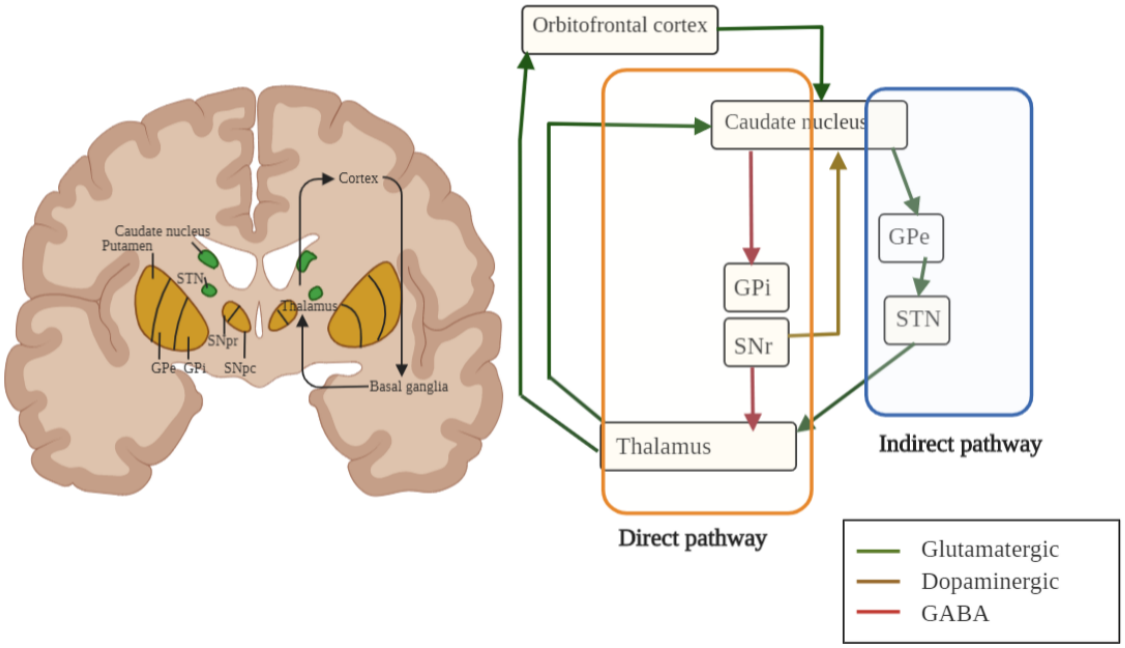


Figure 1: A simplified illustration of the CSTC circuit. *The direct pathway from the striatum (caudate nucleus) is inhibiting the thalamus, the indirect pathway excites the thalamus. The thalamus then excites the OFC by glutamatergic pathways. (Adapted from Robertson et al., 2017)*

The same brain regions that engage in OCD pathophysiology engage in goal-directed behavior (mainly the PFC areas). OCD patients indeed struggle with this type of behavior and they rely too much on habits, resulting in compulsive behavior (Gillan et al., 2011). The ACC and dorsolateral prefrontal cortices (DLPFC) are found to be more active in OCD patients, alongside with higher levels of glutamate in these structures (Gao et al., 2019). This change may cause a shift of cognitive control seen in OCD patients by overactivation of error monitoring systems, including decision – making processes, cognitive interference, planning, and performing motor response (Schlösser et al., 2010). The CSTC loops are now considered as more interconnected. OFC is segregated to functional subdivisions. The overactive lateral OFC can cause

obsessions and inadequate activation of medial OFC may mediate perseveration of behavior.

2.2.2 The limbic system

Even though the aforementioned heuristic model is still valid, there have been some adaptations recently. The limbic system is given greater importance today, due to its communication with the OFC and ACC and related impact on fear, anxiety, memory formation and cognitive flexibility in patients with OCD (Milad & Rauch, 2012). However, the results are very heterogeneous, and I will briefly review the current research on this topic.

The limbic part of BG (ventromedial caudate, ventral putamen, nucleus accumbens, and ventral pallidum) is strongly connected with the amygdala, OFC and ACC and thalamus. Sensory inputs travel to the primary sensory cortex and from there via the fornix to the hippocampus and mammillary bodies (MB) (Aouizerate et al., 2004). The MB informs the hypothalamus to create an affective response and through the anterior nucleus of the thalamus and subsequently ACC to express emotion. ACC then creates a feedback loop to the hippocampus. Consequently, the limbic system connects emotional and affective behavior by selecting and planning action (Aouizerate et al., 2004). According to fMRI studies, the fronto-striatal connection seems to be attenuated and vice versa the hippocampal circuitry potentiated (Rauch et al., 2007; Van Den Heuvel et al., 2005).

In the ENIGMA project, a large meta-analysis of structural changes in OCD patients resulted in the finding that OCD patients have larger GP (supporting the CSTC disruption theory), but a smaller hippocampus in contrast with healthy controls (Boedhoe et al., 2017). Deformation in shape (Hong et al., 2007) and abnormal activation of the hippocampus was observed in OCD patients during reward-based and

implicit sequence learning (Marsh et al., 2015; Rauch et al., 1997). The hippocampal volumes are also different in patients within different symptom categories. Ordering/checking and washing symptoms are more correlated with a decrease in hippocampal volume (Reess et al., 2018). This can be mediated by processes related to stress, considering smaller hippocampal volumes were found previously in patients with stress-related disorders such as PTSD (Ahmed-Leitao, Spies, van den Heuvel, & Seedat, 2016) or depression (McKinnon, Yucel, Nazarov, & MacQueen, 2009). Also, a lower ratio of N-acetyl-L-aspartate/choline in the hippocampus index was reported in patients with OCD, suggesting loss of neurons and axons (Atmaca et al., 2009).

Additionally, OCD symptoms are often accompanied by anxiety and tend to be provoked by anxious situations. Even though there is still not a clear picture of whether the anxious obsessions are creating compulsions or the other way around, it is undeniably an important comorbidity (Gillan & Sahakian, 2015). Anxiety is often characterized as an interruption in inhibitory control proceeded by the lateral PFC, creating a disability to stop disturbing processing without the presence of threat (Bishop, 2009; Sadeh et al., 2015). However, hippocampal hyperactivity has been featured in many anxious/PTSD/depressive patients as well. GABAergic neurons in the hippocampus form a connection with the DLPFC and create an inhibitory fronto–hippocampal control pathway for repressing unwanted thought. DLPFC downregulates hippocampal activity, to induce the repression of those thoughts, however, whether this induction will be implemented depends on GABA inhibition of hippocampal retrieval of mental content. Therefore, inadequate GABAergic transmission in the hippocampus or disruption in the fronto-hippocampal inhibitory pathway may cause insufficient inhibition of unwanted thoughts (Schmitz, Correia, Ferreira, Prescot, & Anderson, 2017). There are also described anxiety cells in the ventral CA1 subregion of the hippocampus (Jimenez et al., 2018). These cells project to the lateral hypothalamus and their position is in line with anxiolytic effects of lesions in the ventral hippocampus (Bannerman et al., 2002). Connections from the hippocampus to the middle temporal

gyrus (MTG), anterior cingulate gyrus (ACG), and the cerebellum were amplified in patients with OCD in comparison with healthy controls. The hippocampal network and its strength have an impact on the relationship between anxiety and obsessions and may have a role in differentiating specific symptom dimensions. The connection between the hippocampus and cerebellum may be involved in monitoring and awareness deficits in OCD. The ACC-hippocampus connection is responsible for error processing. The MTG is impaired in patients with OCD, with higher hippocampus-MTG connectivity and higher grey matter volume, disabling a patient´s suppression of intrusive thoughts and producing anxiety (Li et al., 2020). The compulsive behavior produced by quinpirole is associated with a decrease of hippocampal plasticity-related activation (Brozka et al., in preparation). The hippocampal network and mainly the hippocampal-temporal and hippocampal-frontal connection may have an impact on anxiety and OCD symptoms and create new treatment possibilities (fig.2) (Li et al., 2020).

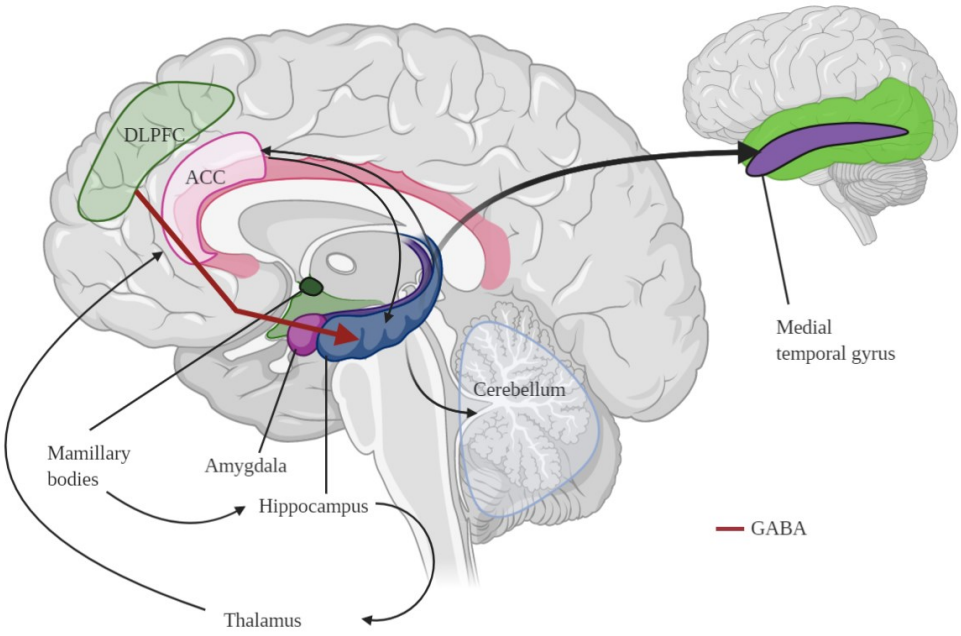


Figure 2: A simplified illustration of the fronto-limbic connection. *The connection from the hippocampus to medial temporal gyrus (MTG) is strengthened in OCD patients, disabling patients to stop unwanted thoughts. The connection from the dorsolateral-prefrontal cortex to the hippocampus creates a fronto-hippocampal control pathway for the repression of those thoughts. (Adapted from Li et al., 2020).*

Inactivation of the ventral hippocampus by silencing glutamatergic projections to the nucleus accumbens promotes flexible behavior in rats expressing G_i-coupled DREADD in the ventral hippocampus. The silencing was done by infusing its agonist CNO (clozapine-N-oxide) (Barker, Bryant, & Judson Chandler, 2019). This agrees with findings of higher hippocampal activity seen in OCD patients after individual symptom provocation in fMRI (Adler et al., 2000) and lower hippocampal activity after treatment with SSRIs (Kang et al., 2003). Hence, overactivation of the hippocampus can create habitual behavior and the suggested role of the hippocampus in OCD is by recent

findings furthered and maybe be directly involved in the pathophysiology instead of only compensating for the insufficient cortico-striatal circuits (Ullman & Pullman, 2015).

Overall, recent findings suggest high interconnection of frontal structures to the limbic system gives significant importance to the hippocampus and its network projections. This may in time give a clearer picture of symptom dimensions and their differences and create a new possibility for prescribing and developing medication.

2.3 Neurochemistry of OCD

2.3.1 Serotonin in OCD

The role of serotonin (5-hydroxy-tryptamine, 5-HT) in OCD pathogenesis was first brought up by effective treatment with SRIs as mentioned above. 5-HT is involved in the regulation of hormone secretion, immune system, energy balance, vigilance, and the regulation of other basic physiological functions. The phasic activation of 5-HT neurons is correlated with the rhythmicity of behavior and movement. Through affecting glutamatergic, GABA, and dopaminergic transmission, 5-HT controls cognitive, behavioral, and motor outcomes in animals (Ciranna, 2006).

Alongside with polymorphism in the gene coding catechol-*o*-methyl transferase (COMT) or monoamine oxidase A, associations between OCD and polymorphism in gene coding $5HT_{2A}$ (Enoch et al., 1998), $5\text{-}HT_3$ (Kim et al., 2016) and $5HT_{1D\beta}$ (Mundo, Richter, Sam, Macciardi, & Kennedy, 2000), the gene for SERT (serotonin transporter) (Murphy & Lesch, 2008; Sinopoli, Burton, Kronenberg, & Arnold, 2017) and some others (Derksen, Feenstra, Willuhn, & Denys, 2020) have been reported. Therefore, it appears, that development of OCD symptoms is moderately affected by several different genes related to 5-HT function.

Agonizing 5-HT receptors with mCPP (meta-chlorophenyl piperazine) has been shown to lead to exacerbation of OCD symptoms in humans as well as in animal models of OCD (Marazziti, Hollander, Lensi, Ravagli, & Cassano, 1992). Nevertheless, using a pure 5-HT_2 antagonist ritanserin exerted the same effects (Erzegovesi, Ronchi, & Smeraldi, 1992), and treatment with 5-$HT_{1A/2A/2C}$ receptor agonist psilocybin reduced acute OCD symptoms successfully (Moreno, Wiegand, Taitano, & Delgado, 2006). This variability in outcomes may be explained by different specificity of drugs to serotonergic receptors. The agonist of 5-$HT_{1A,\ 1D,\ 2A,\ 2C}$ receptors mCPP is also antagonizing 5-HT_3 and adrenergic α2 receptors. Though there is not a clear view of the specificity of 5-HT receptors and how they mediate OCD behavior, their involvement is apparent (Rauch & Jenike, 1993).

Neurochemically, 5-HT synthesis is increased in OCD patients, SERT binding is decreased in thalamic and hypothalamic areas, both factors relate to symptom severity (Kim et al., 2016). Earlier the idea was, that SSRIs modulate the 5-HT system and hence compensate dysfunction in other neurotransmitter systems. However lately, with genetic and binding studies, there is possible causation of serotonergic dysfunction in OCD patients (Derksen et al., 2020).

2.3.2 Dopamine in OCD

The dopaminergic (DA) system has several functions in the human brain. Dopaminergic neurons in substantia nigra (SN) project to the striatum and plays a role in the motor control in the BG as reviewed above in chapter 2.2.1., from the ventral tegmental area (VTA) to frontal cortex projections affect learning and memory and from VTA to the limbic system creates the reward and motivation circuit. All of these are closely related to the CSTC and frontotemporal circuitry.

Dopaminergic involvement in OCD was first brought up by Goodman (1990) because of an interaction between the 5-HT and DA system. The increase in dopaminergic tone and downregulation of DA receptor expression /function may be a result of serotonergic deficiency. Indeed, haloperidol or risperidone (DA antagonists) addition to fluvoxamine treatment augmented therapy in OCD patients (Goodman et al., 1990; McDougle et al., 1994). Higher dopamine transporter density was found in OCD patients without comorbidities (Van Der Wee et al., 2004). A decrease in D_2/D_3 receptors binding in the striatum, probably due to dopaminergic hyperactivity in OCD patients was observed as well (Denys et al., 2013). This concept is also supported by an ability dopamine D2/D3 agonist quinpirole to produce compulsive checking and deficits in flexibility and learning in an animal model for OCD (Szechtman, Sulis, & Eilam, 1998a; Hatalova et al., 2014, Janikova et al., 2019).

Dopaminergic D1 receptors are also located on neurons of the direct pathway of the CSTC circuit and they act proconvulsive (Starr, 1996). In the state of dopamine release, D1 receptors activate the direct pathway. Their agonizing has produced OCD-like symptoms in mice and increased extracellular levels of GABA and glutamate (Abekawa, Ohmori, Ito, & Koyama, 2000). On the other hand, D_2 receptors are mainly located on the indirect pathway and their activation inhibits the inhibition (disinhibits) of the indirect pathway. Conclusively, in both these pathways, dopamine facilitates the activation of cortical structures (Gerfen & Surmeier, 2011).

2.3.3 Glutamate in OCD

Glutamate is the primary excitatory neurotransmitter in the brain, and it plays a primary role in the CSTC circuit as well. The glutamatergic system seems to be functionally disrupted in patients with OCD (Rotge et al., 2010; Ting & Feng, 2008). Greater glutamate concentrations were found in the cerebrospinal fluid (Chakrabarty, Bhattacharyya, Christopher, & Khanna, 2005) and the caudate nucleus and lower in

ACC in both pediatric and adult OCD patients (Rosenberg et al., 2000, 2004). Additionally, in adult patients, greater OFC glutamate concentrations were found (Whiteside, Port, Deacon, & Abramowitz, 2006). These results suggest that overactivation of the striatum and the OFC in combination with the hypoactivity in the ACC may create a tonic-phasic dysregulation of the circuit (Wu, Hanna, Rosenberg, & Arnold, 2012b).

Genetically, several candidate genes coding glutamatergic transporters and receptors have been found to have OCD-like effects when deleted/inhibited. These include SLC1A1, reviewed above, GRIN2B (Arnold et al., 2004) coding an NMDA receptor subunit, or SAPAP3. SAPAP3 is a scaffolding protein, whose deletion intensifies anxiety-like behavior and compulsive grooming in the rat (Welch et al., 2007). Compulsive behavior may be a consequence of bursts of glutamatergic activity in specific areas of the brain (Monteiro & Feng, 2016). Disrupted levels of glutamate in the ACC and OFC can over-over-stabilize attractor networks, increase firing rate, and hence creating perseveration of behavior, which is hard to escape and switch (Rolls, Loh, & Deco, 2008). Therefore, glutamate modulating drugs are studied to help to switch from one behavior to another and lift the increased stability of the attractor system. Anti-glutamatergic agents, working as glutamate receptor antagonists or channel blockers can decrease glutamate levels in the CSTC circuit and hence be beneficial for treatment (Wu et al., 2012b).

Beyond riluzole and memantine used in this study and reviewed below, other drugs were found effective in alleviating OCD symptoms. They have a different mechanism of action and work via different paths. Among others, these include amantadine, both dopamine agonist and antagonist and NMDA receptor antagonist, D-cycloserine (Kushner et al., 2007; Wilhelm et al., 2008) working as a partial agonist of NMDA receptor at glycine binding site (Norberg, Krystal, & Tolin, 2008) or ketamine, working through antagonization of the NMDA receptor (Rodriguez, Kegeles, Flood, &

Simpson, 2011). However, these are few smaller studies or case studies and none of these drugs are yet commonly prescribed clinically.

Another interesting drug that was studied, due to its antioxidant effects, is n-acetyl cysteine (NAC). It was found to alleviate OCD symptoms in augmentation to fluvoxamine treatment (Lafleur et al., 2006). NAC is an antioxidant and modulates glutamatergic neurotransmission by increasing glutamate in the synapse by acting on the glutamate/cysteine antiporter on glial cells. Surprisingly, this increase of glutamate in synaptic cleft creates negative feedback for the presynaptic cells and reduces glutamate release (Moran, 2005). Effectiveness of NAC has been supported by a finding that elevated levels of overall ROS (reactive oxygen species) were detected in serum from children with OCD (Kandemir, Abuhandan, Aksoy, Savik, & Kaya, 2013).

2.3.4 Glutamate/serotonin interaction

On a presynaptic level, serotonin can modulate the release of other neurotransmitters. Depending on the presence receptor in the presynaptic membrane, it can reduce (5-HT_{1A}, 5-HT_6) or stimulate (5-HT_3) release of glutamate or GABA (5-HT_2). Serotonin can also stimulate postsynaptic sites by boosting receptor synthesis and intervening in membranes and modulating their function by phosphorylation. Also, by 5-HT signaling pathways, it can modulate the activity of ion channels and neuronal excitability (Ciranna, 2006).

In the hippocampus, 5-HT suppresses LTP (long-term potentiation) by preventing AMPA receptor activation. Overall suppression of excitatory neurotransmission after experimental 5-HT infusion might then be the cause for observed memory deficiency in those patients (Staubli & Otaky, 1994). However, these effects are receptor subtype-dependent, as 5-HT_{2A} and 5-HT_4 can activate glutamate release in the dentate gyrus and positively modulate the LTP. Furthermore, 5-HT pre-

synaptically reduces glutamate release in the entorhinal cortex, the origin of one of the main excitatory projections to the hippocampus (Schmitz, Gloveli, Empson, Draguhn, & Heinemann, 1998).

In the frontal cortex, glutamate-serotonin interactions are reciprocal, as 5-HT can inhibit glutamate release and glutamate can induce 5-HT release in raphe nuclei (Fink, Böing, & Göthert, 1996). In cranial motor nuclei, 5-HT activates glutamate excitation of motor neurons. On the other hand, in the red nucleus and the cerebellum 5-HT represses glutamate excitation and modulates motor behavior. This suggests a significant role of this interaction in psychiatric diseases and a possible medical intervention. For example, antagonizing 5-HT_{2B} receptors could be useful in anxiety and memory dysfunction treatment, or antagonizing 5-HT_6 receptors could help with cognitive deficits. 5-HT_{1A} and 5-HT_{2A-C} are reducing excitotoxicity produced by glutamate overactivation (Ciranna, 2006). Antagonizing 5-HT_{2A} receptors can attenuate repetitive behavior and hyperlocomotion by diminishing the blockade of NMDA receptors (Carlsson et al., 1999; Higgins, Enderlin, Haman, & Fletcher, 2003). Finally, in the basal ganglia, 5-HT controls GABA synthesis and release (Di Cara, Samuel, Salin, Kerkerian-Le Goff, & Daszuta, 2003).

Glutamate levels decrease in the PFC and caudate nucleus after treating patients with clomipramine/paroxetine (Moore, MacMaster, Stewart, & Rosenberg, 1998; Saxena, Brody, Schwartz, & Baxter, 1998). Therefore, mechanisms of efficient treatment with SSRIs may lie not only in modulating the serotonergic system but in attenuating glutamate release in the CSTC circuit. Agonizing 5-HT_{2A} receptors lowers the transmission by glutamate (Carlsson, 2000). Supporting this idea, psychedelic drugs (5-HT_{2A} agonists) have been effective for OCD treatment as well, thus reduction in glutamate levels may be one of their pathways of action (Leonard & Rapoport, 1987).

2.3.5 Other neurotransmitters in OCD

The complexity of brain circuitry and neurotransmitter systems is enormous, therefore definitely several other neurotransmitters and neuromodulators play a more or less significant role in the pathophysiology of OCD. Oxytocin, a hypothalamic hormone, is critically involved in maternal behavior. However, it influences many other behaviors, such as grooming, cognitive and sexual behavior. Elevated levels of oxytocin were found in the plasma of OCD patients (Marazziti, Baroni, Mucci, & Dell'Osso, 2016), and mice and rats with artificially increased oxytocin levels increased self-grooming behavior was observed (Kaltwasser & Crawley, 1987). The oxytocin receptor (OXTR) is potentially involved in the genetic base of OCD, with multiple variants of OXTR having different effects on the OCD onset age (Kang, Kim, Kim, Hwang, & Kim, 2017). Furthermore, OXTR can be methylated at some critical period of life development, and this hypermethylation of OXTR has been found in OCD patients, not in healthy subjects (Cappi et al., 2016). Some other neurotransmitters were studied as well, such as progesterone and estrogen, which appear to influence serotonin signaling (Karpinski, Mattina, & Steiner, 2017) or arginine-vasopressin (Rutigliano et al., 2016).

Together, there is compelling evidence for the involvement of serotonergic, dopaminergic, and glutamatergic systems in OCD. Nevertheless, future research is needed along with more research on less studied neurotransmitters and their possible influence. The cortico-striatal and cortico-temporal connections are highly complex; their understanding will be greatly beneficial for basic and subsequent clinical research and finding new therapies. In the end, it could result in a valuable help in treatment for people with OCD.

2.4 Properties and effects of drugs used in this study

2.4.1 Riluzole

Riluzole (2-amino-6-(trifluoromethoxy) benzothiazole) was developed as an anticonvulsive drug. It is now officially used for patients with amyotrophic lateral sclerosis (ALS), to which it prolongs time without the need for a respirator. It is also used for the treatment of other psychiatric conditions, however, in these cases, riluzole is prescribed off-label. Given its glutamate-modulating, anticonvulsant, and neuroprotective properties, it makes a promise to be used in mood and anxiety-related diseases, such as OCD (Zarate & Manji, 2008).

Pharmacokinetics of riluzole is the following: 90 % of it is absorbed, the total bioavailability, when taken orally, is 60 %. Excretion is mainly through urine with a half-life from 9 to 12 hours (Viswanad, 2017). Riluzole acts as a glutamatergic antagonist, however, its specific mechanisms of action are not yet fully understood. Nevertheless, it seems that is has a complex range of functions, such as increasing clearance and decreasing the presynaptic release of glutamate and antagonizing its receptors. It was shown that it normalizes sodium channels, reduces excitability, and stimulates the growth of neurons (Gaber, Mehmood, & Siringwani, 2016). Neuroprotective abilities of riluzole have been tested *in vitro* (Malgouris & Doble, 1994), as well as in animal models in vivo (Meldrum & Garthwaite, 1990). Neuroprotectivity may be caused by its interference with G-protein signaling pathways, like those activated by adenosine A1 and GABA b receptors.

It interferes with many ion channels, for example with chloride channels, calcium channel, mammalian TRAAK (TWIK Related Arachidonic acid Activated K + channel) channel, in cortical neurons it regulates the Na^{2+} and K^{+} currents (Meininger, Lacomblez, & Salachas, 2000). Riluzole was found to be effective in increasing GLT1 (glutamate transporter subtype 1), an excitatory amino acid transporter 2 (EAAT2)

(Rothstein et al., 1996), EAAT1 (GLAST; glutamate-aspartate transporter) activity (Fig 3). These two transporters are remarkably effective in preventing the accumulation of glutamate in extrasynaptic space by boosting the uptake of glutamate, hence protecting neurons from neurotoxic effects of glutamate (Fumagalli, Funicello, Rauen, Gobbi, & Mennini, 2008). Riluzole probably changes the relative affinity of these transporters to glutamate. It also increases the expression of the AMPA receptor subunits GLUR1 (glutamate receptor type 1) and GLUR2 (glutamate receptor type 2) (Du et al., 2007). High concentrations of riluzole are antagonizing AMPA, kainate, and NMDA receptors (Pittenger et al., 2008). Other neurotransmitters may be altered by riluzole as well. Decrease of acetylcholine and dopamine release was observed (Albo, Pieri, & Zona, 2004), on the other hand, GABA- and glycine-hyperpolarization can be potentiated by riluzole (Mohammadi, Krampfl, Moschref, Dengler, & Bufler, 2001).

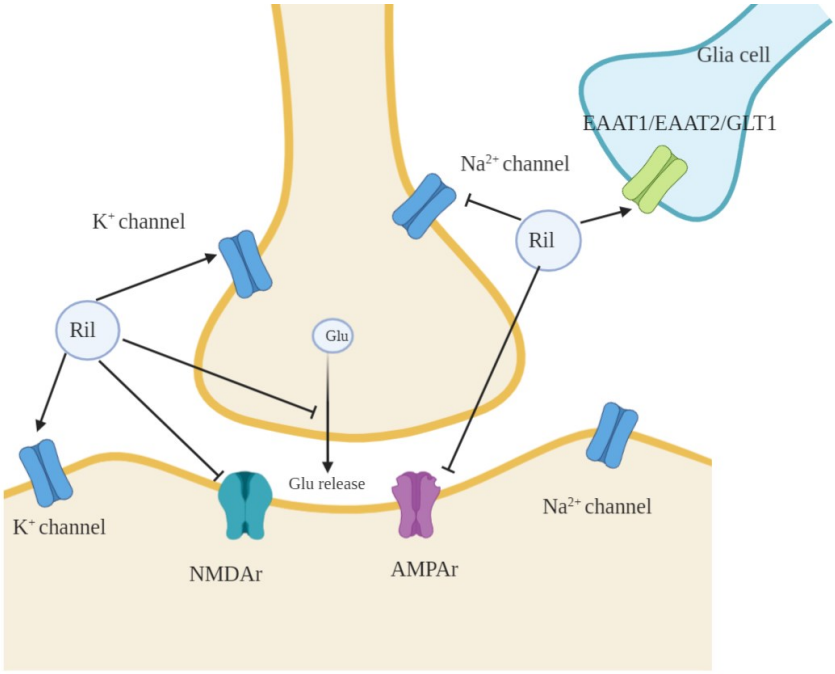


Figure 3: The possible effects of riluzole on glutamatergic transmission in the synaptic cleft. *Riluzole inhibits NMDA and AMPA receptors (however, enhances AMPA receptor subunits expression). It inhibits glutamate release, possibly by modulation of ion channels, and increases glutamate transport from the synaptic cleft to glial cells. (Adapted from He et al., 2002).*

Due to its wide range of effects and relatively safe profile with low reporting of adverse side effects, riluzole has been in several clinical studies including patients with unipolar and bipolar depression, generalized anxiety disorder (GAD), cocaine dependence, and OCD (Zarate & Manji, 2008). Many case reports were useful in alleviating OCD, major depressive disorder (MDD), or bipolar disorder symptoms (Ciraulo et al., 2005; Grant et al., 2014; Ibrahim et al., 2012; Park et al., 2017).

In an open-label trial with OCD children, scores in CYBOCS (Children Yale-Brown Obsessive-Compulsive Scale) improved by 39% after riluzole administration. After double-blinded placebo trial with children (7-17 years), most of the participants

chose to take open-label riluzole and some of them had discontinued all their other medication (Grant et al., 2010), even though, riluzole showed no greater efficiency than placebo (Grant et al., 2014). In a placebo-controlled study with outpatients and inpatients, riluzole showed efficiency in alleviating OCD symptoms in some of the patients, however, it was not significant in overall statistics. Nevertheless, it can be beneficial for some patients (Pittenger et al., 2006). In a double-blinded, randomized, placebo study with riluzole/or placebo being administered together with fluoxetine, results showed a reduction in total Y-BOCS scores in riluzole group, with a difference in Y-BOCS obsessive and compulsive scales. The reduction of obsessions was not significant, although compulsions where downscaled considerably (Emamzadehfard et al., 2016). A case report from 13 treatment-refractory patients, scoring exceedingly high on general Y-BOCS, showed promising results. Significant symptom reduction in self-evaluation, as well as in Y-BOCS scale (max. 50% reduction), reported 7 of them (Pittenger, Kelmendi, Wasylink, Bloch, & Coric, 2008).

Riluzole did not affect the quinpirole animal model of OCD, which can be explained by potentiating, rather than antagonizing effects, of these two substances (Janikova, Brozka, Radostova, Svoboda, & Stuchlik, 2019). Quinpirole was found to increase glutamate concentrations in SNr and striatum (Abarca, Gysling, Roth, & Bustos, 1995), however, it also decreases glutamate levels in the NAc (Escobar et al., 2015). Lesions to the nucleus accumbens produce stereotypic behavior and memory problems. Consequently, when riluzole normalized levels of glutamate in SNr and striatum, it also, even more, decreased its levels in NAc and exacerbated some effects of quinpirole (Janikova et al., 2019).

Riluzole´s relatively safe profile and some positive effects on MDD, OCD, and more, make it in need to be evaluated in future research. Recent results are in a slight score in the positive balance for its use in psychiatric disorders including OCD.

2.4.2 Memantine

Memantine is a non-competitive low-affinity NMDA receptor (NMADr) antagonist. It is an open-channel blocker; thus, it blocks the current flow by blocking the channel after the receptor pore is open. Afterward, agonist unbinds and memantine is trapped inside, blocking the receptor (Fig. 4). Memantine can bind to two specific sites of NMDAr and it probably competes with $Mg^{2+,}$ which means that it affects only on relatively depolarized neurons (Johnson & Kotermanski, 2006).

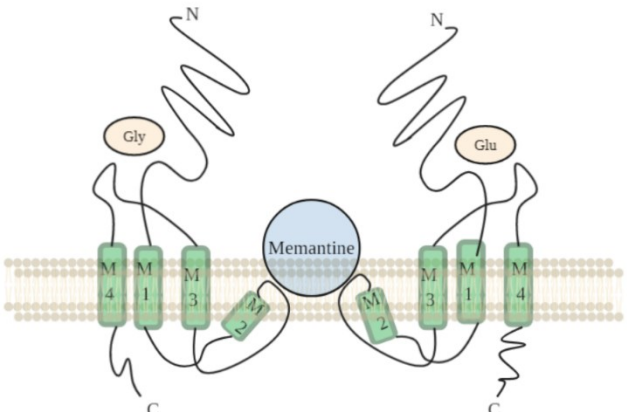


Figure 4: Memantine binding site on NMDAr. *(Adapted from Johnson & Kotermanski, 2006).*

Memantine has rapid kinetics of unblocking the channel, therefore it does not pathologically alter glutamate neurotransmission. This may be a reason for the differences between memantine and other NMDA receptor antagonist, such as ketamine, which has serious adverse side–effects and induced psychosis and with increasing dose, anesthesia (Witt, Macdonald, & Kirkpatrick, 2004). Other possible differences in effect may be NMDAr subtypes preference, voltage dependence, and faster and stronger inhibition under higher glutamate agonist concentrations. Memantine probably does not bind to all receptors available at that moment (Johnson & Kotermanski, 2006), and it can bind to specific subtypes of NMDAr such those in extrasynaptic sites, whilst ketamine binds to synaptic receptors (Johnson, Glasgow, & Povysheva, 2015). Memantine and ketamine have been found to have different desensitization effects at the NMDA receptors. Memantine stabilizes Ca^{2+}-desensitized

state of GluN1/2A receptors, hence increasing Ca^{2+} concentrations intracellularly. Ketamine decreases the occurrence of desensitized states of GluN1/2B receptors. This could explain the variance between subpopulations of NMDAr and it proposes new strategies for pharmaceutical research for Ca^{2+} dependent desensitized states (Glasgow, Povysheva, Azofeifa, & Johnson, 2017). Memantine shifts the excitation-inhibition balance in the prefrontal cortex to more excitation and it does so by inhibiting interneurons firing on excitatory neurons (Povysheva & Johnson, 2016). This mechanism is very subtle, and since most of the inhibitory and excitatory neurons are dependent on NMDAr in terms of activity and plasticity, only a small change/or small difference in changes may create various outcomes. The balance between synaptic and extrasynaptic activation of NMDAr is responsible for signaling to the cell whether it will die or survive, hence the small difference between so similar molecules, such as ketamine and memantine, is crucial (Johnson & Kotermanski, 2006).

Memantine was initially developed to reduce blood sugar (Gerzon, Krumkalns, Brindle, Marshall, & Root, 1963), which did not work. Later, it was found to have effects on the CNS (Grossmann & Schutz, 1982) and to behave as an NMDA receptor antagonist (Bormann, 1989). At the time, memantine was introduced to dementia treatment and is still commonly used for severe Alzheimer's disease. It helps to increase cognitive functions in patients with AD and facilitates daily functioning (Witt et al., 2004).

In the treatment of OCD, several case reports have shown the efficacy of memantine for OCD patients, those who did not respond well to previous medication. Probably, the first case of successful memantine use for OCD patients (adult women with fear of harm and checking compulsions) was described by Pouyrovsky (Poyurovsky et al., 2005). Subsequently, memantine was found effective in another patient with checking compulsions; however, not in a patient obsessed about contamination (Pasquini & Biondi, 2006). In a meta-analysis of double-blinded,

placebo-controlled, randomized studies made by Kishi (2018), memantine was valued as a valid treatment for patients with SSRIs-refractory OCD symptoms. Nevertheless, there were not any long-term studies in this analysis, so the effectiveness of memantine in such terms has not been thoroughly examined yet (Kishi, Matsuda, & Iwata, 2018a). Interestingly, in one study, memantine was administered after the single infusion of ketamine (Rodriguez et al., 2016). The sample was small and ketamine itself had particularly beneficial effects on OCD symptoms in some patients, however, in many, no effect was observed. Following the administration, memantine had no effect on patients that did not respond to ketamine. On those that had responded well to one-dose ketamine treatment, oral memantine may have helped to persist the ketamine effect, however, it is not clear whether ketamine itself could not have these long persistent effects. This might suggest that there are patients not responding to NMDAr modulators at all (Rodriguez et al., 2016).

Adding memantine to the maximum tolerated SRI's dosage significantly improved scores in Y-BOCS scales in refractory OCD patients. Memantine has very insignificant side-effects and well tolerability given together with its quite interesting effectiveness in treatment-resistant OCD patients, memantine is a promising drug to be used within OCD for augmentation with SRIs or even as a monotherapy option (Modarresi et al., 2018).

2.5 Animal models

Animal models are of significant use in all biomedicine, no less in neuroscience. They are suitable for a better understanding of the basics of mechanisms that control normal and abnormal behavior, hence for the brain-behavior relationship, for transforming knowledge to the clinic, identifying new drug targets and evaluating drugs that could be helpful (Van Der Staay, Arndt, & Nordquist, 2009). To validate the

usefulness and comparability of animal models, three axes of validity must be fulfilled: face validity, predictive validity, and construct validity.

Face validity is a degree of similarity between a behavior seen in the animal and the human disabled with a given psychiatric disease. Although this is pushed to be the most important criterion, it can be anthropomorphically validated and animals can have species-specific behavior with different psychological underlying mechanisms (Holmes, 2003). Predictive validity is a prediction about the behavior in a situation that it is supposed to model, it allows for the effect of manipulation to be transferable in time, space, and species. This criterion is mostly used for evaluating the ability to react to drugs/treatment and for molecular targeting. Construct validity reflects resemblances between underlying mechanisms of behavior in the model and the disease in humans. It considers neurological, pathological, and behavioral mechanisms (Belzung & Lemoine, 2011).

According to van der Staay (2009), external validity and replicability should be taken into consideration when creating a model as well. External validity expresses how the model can be generalized across species/populations of species. Replicability is the ability of the model to be used multiple times in different laboratories by different scientists. It gives the model statistical strength when it is replicable.

Animal models of OCD are mainly modeling compulsive behavior which is seen as stereotypic/repetitive behavior. The behavior is then analyzed and the structure of it is taken into consideration, giving an insight into the circuitry od genetic bases of the disease. There are several types of OCD animal models and I will review them briefly and then I will focus on the 8-OH-DPAT animal model used in this study.

2.5.1 Ethologic models

Ethologic or behavioral models are naturally and spontaneously occurring behaviors, that are not induced by pharmacological, genetic, or any other invasive procedures. This includes marble burying, tail chasing, grooming, picking, etc. These behaviors correlate with human actions such as hair pulling, extensive washing, repetitive movements, and others.

2.5.2 Barbering and excessive grooming

Barbering is extensive picking of hair from a cagemate or the animal itself. It is observed in laboratory rodents and since that is not something usually observed in other animals, it is a particularly good correlation to human trichotillomania, which is an extensive picking of own hair. This behavior is often seen in OCD patients, with most trichotillomania patients being women, with symptoms onset in puberty. This bias has been observed in laboratory animals as well (Garner, Weisker, Dufour, & Mench, 2004). Excessive grooming is characterized by unnecessary licking of skin that can cause dermatitis and skin lesions. This behavior is often seen together with the anxious behavior of an animal. Excessive grooming is an animal trait existing through most mammals, comparable to washing and cleaning obsessions and compulsions in humans. In laboratory animals, excessive grooming is alleviated when SRIs are administered, thus this model has good predictive and face validity (Wynchank & Berk, 1998). This behavior can be naturally occurring, or it can be induced by various agents (transgenic – mouse with deficits in SAPAP3 proteins, pharmacological)

2.5.3 Marble burying

Rodent behavior of moving objects and hiding them has been used to test anxiety-like behavior repeatedly. Rodents bury objects to the bedding, which are potentially harmful or noxious. However, there have been many observations of rodents

hiding objects, that were not in any way harmful (glass marbles) for them and thus it may not be solely a fearful behavior and can be associated with an investigative activity as well. The repetition of this behavior can be produced by the rodents when they do not receive a suspected outcome and investigative behavior repeats. The suspected outcome is in this case the fact, that the marbles do not create any reaction to the rodents' action (Londei, Valentini, & Leone, 1998). Several SRIs and SSRIs are effective in alleviating marble burying, however, some antipsychotic drugs were effective as well, which decreases predictive validity for the marble burying test as an OCD model, because antipsychotic drugs as monotherapy do not usually alleviate OCD symptoms in human patients (Broekkamp, Rijk, Joly-Gelouin, & Lloyd, 1986). Glutamatergic modulators amantadine and memantine (see below) alleviated marble-burying behavior, thus suggesting a treatment option of these substances for further studying (Egashira et al., 2008).

2.5.4 Food-restriction induced hyperactivity (FRIH)

Giving food only one time a day to a rat, instead of having food available ad libitum, it begins to run excessively on a running wheel and eat even less food and lose weight rapidly. This hyperactivity is explained as an adjunctive behavior that is being caused by the stress-induced by food restriction. Such behavior is seen throughout species as a reaction to different stressful stimuli. This model has good predictive validity because FRIH is attenuated with fluoxetine (SRIs) and not attenuated with imipramine (TCA). Both these drug effects are observed in OCD patients (Altemus, Glowa, Galliven, Leong, & Murphy, 1996).

2.5.5 Signal attenuation

Theoretically, compulsions result from unsatisfactory outcome from the action, impaired processing of feedback information. The signal attenuation model is based on

this mechanism. Rats are given food after lever pressing, alongside with presenting an external stimulus. Subsequently, there is no food presented, only the external stimulus after pressing the lever. Thus, attenuating the association strength between reward and external stimulus feedback after completing the operant task. The animals, that were not getting food so often after pressing the levels, were more likely to press the lever more often – compulsively (Joel & Avisar, 2001). SSRIs (Joel, 2006) and D-cycloserine (DCS), an NMDA partial ligand at the glycine binding site (Albelda, Bar-On, & Joel, 2010) have attenuated this behavior.

2.5.6 Spontaneous stereotypy

The deer mouse (*Peromyscus maniculatus bairdii*) is an animal with a naturally occurring stereotypic behavior such as flipping, jumping, or running in patterns. This behavior is environment-dependent; deer mice tend to act more stereotypically and over-ritualize in a small cage with fewer stimuli. Administrating MK-801, NMDA receptor antagonist and SCH23390, D1 receptor antagonist, attenuated this ritualization with no further attenuation of other behavior. D1 receptors are located on medium spiny neurons of the striatum and their activation makes them more sensitive to excitatory cortical and thalamic projections. Therefore, when D1 receptors are blocked, the activity in the positive feedback circuit is decreased. These findings support the CSTC circuit theory of stereotypic behavior (Presti, Mikes, & Lewis, 2003).

2.5.7 Genetic models

Genetically modified animals are usually generated based on the theoretical genetic mutations or variants associated with specific symptoms (viz. chapter 2.1). The deletion of the SAPAP3 gene causes increased anxiety and grooming, which are alleviated with fluoxetine. Hoxb8-KO mice are prone to excessive grooming (themselves and cagemates too), creating massive lesions on their bodies, which have

no skin-deficit reasons. Hoxb8 factor is expressed in microglia migrating to brain areas related to the CSTC circuit. Transplantation of bone marrow from wild type mouse to Hoxb8-KO decreases the harmful grooming. This suggests a link between the immune system and OCD (Chen et al., 2010) and resonates with the PANDAs theory (Murphy, Kurlan, & Leckman, 2010). Mice with a knock-out of 5HT2c receptor acted compulsively (Chou-Green, Holscher, Dallman, & Akana, 2003), their locomotor activity and risk assessment behavior were elevated compared to wild-type animals (Nebuka et al., 2020) and increased firing of dopaminergic neurons in SNc and associated behavior was observed. With that, the deletion of 5-HT2c increased stereotypical behavior induced by psychostimulants (Abdallah et al., 2009). Nigrostriatal transmission is, as reviewed above, an important part of the CSTC loop, hence suggesting straightforward importance in OCD pathophysiology.

2.5.8 Pharmacologic models

Using well-selected pharmacologic agents to model neurochemical and behavioral disbalances leans towards having a model with good predictive, construct, and face axes of validity. The selection of drugs is based on a theoretical involvement or neurotransmitter systems in a specific disease and then chronically or acutely administering agonists or antagonists on selected receptors. In pharmacological models of OCD, drug-inducing behavioral changes are resembling human behavior associated with OCD diagnoses, such as perseverative and stereotypical behavior or compulsive checking. Pharmacologic models should react to the same treatment as human patients do, hence supporting the predictive validity of the model (Nestler & Hyman, 2010).

2.5.9 mCPP

The active metabolite of antidepressants, mCPP (1-(3-chlorophenyl)piperazine) is extensively used for modeling psychiatric conditions given its strong effects on

presynaptic and postsynaptic sites of the serotonin system (Kahn & Wetzler, 1991) and very little effect on the dopaminergic system (Eriksson, Engberg, Bing & Nissbrandt, 1999). Initially, mCPP stimulates serotonin release from the presynaptic site (Pettibone & Williams, 1984), and then it agonizes 5-HT2C receptors and moderately also to other 5-HT receptors. Pre-treatment with citalopram (Eriksson et al., 1999) or fluoxetine (Tsaltas et al., 2005), SRIs, used for OCD treatment, inhibit mCPP effects. It is also used as a drug of abuse as well given the similarities to MDMA, both of them working on SERT (serotonin transporter) (Bossong, Van Dijk, & Niesink, 2005), and has shown to exacerbate symptoms in OCD patients as well as in patients with other anxiety disorders (Pigott et al., 1993). In an animal model, mCPP increases persistent behavior in a T-maze (Tsaltas et al., 2005).

2.5.10 Clomipramine – a neurodevelopmental model

Clomipramine is used as a treatment for OCD symptoms, however, administration of clomipramine to rats in an early-postnatal time produces significant changes in adulthood, thus creating a neurodevelopmental model. Rats treated with clomipramine early in their lives were more anxious on elevated plus maze and in a marble burying test, they had memory deficits and were more persistent and showed overall decreased behavioral flexibility. Additionally, D2 receptors in the striatum and 5-HT2c receptors in OFC were elevated, demonstrating an alteration in the CSTC circuit. With its multiple symptom effect and neurochemical changes, this creates a very valid model of OCD and at the same time giving an insight into developmental changes and possible treatment strategies. This study was done on Sprague-Dawley rats (Andersen, Greene-Colozzi, & Sonntag, 2010), however, pilot data from our lab on Long-Evans rat did not show any effectiveness of clomipramine postnatal treatment in creating a model of OCD (Valigová, n.d.).

2.5.11 Quinpirole model of compulsive checking

Quinpirole is a D2/D3 receptor agonist, and its chronic administration to rats leads to stereotypic behaviors and a path stereotypy. In an open-field arena enriched with several objects, they revisit specific locations and return to a selected object(s) faster and more frequently than a healthy control, presumably by enhancing the motivational state in a CSTC circuit (Alkhatib et al., 2013). Clomipramine partially attenuates this behavior, most likely for its dopamine-blocking properties. This partial relief of symptoms corresponds with many OCD patients that respond to SRI treatment only to some extent as well. Hence creating a good predictive and face validity (Szechtman, Sulis, & Eilam, 1998b). Interestingly, quinpirole alters the glutamatergic system as well, supporting the theory of glutamate involvement in OCD. Evidence also suggests altered glutamate extracellular levels in OCD patients (Figee et al., 2011). Chronic quinpirole administration causes the desensitization of D2 receptors which decreases metabolism in caudate-putamen and hippocampus (Servaes et al., 2016). By labeling a raclopride molecule (D2 antagonist competing with quinpirole for its binding site) with a radioactive isotope, reduced binding sites for D2 agonists in chronically sensitized rats to quinpirole were shown, indicating internalization of receptors or development of tolerance. In the CSTC circuit, levels of mGlu5 receptors were higher after chronic treatment with quinpirole, suggesting a dopamine-mediated inhibition of glutamate release was constrained by quinpirole (Servaes, Glorie, Verhaeghe, Stroobants, & Staelens, 2017) These outcomes give rise to a possibility to test glutamatergic agents on this model, such as memantine and riluzole. Nevertheless, a recent study done by our research group showed no improvement of quinpirole-induced symptoms, but on the contrary, a potentiating effect of memantine and riluzole. The possible reason for this action is the quinpirole-mediated inhibition of glutamatergic activity in the NAc; therefore, other glutamate antagonists exacerbated the symptoms instead of alleviating them (Janikova et al., 2019). In the present study, we tested these drugs on a model formed by 8-OH-DPAT, which acts on the serotonergic system.

2.5.12 8-OH-DPAT model of compulsive checking

A potent selective 5-HTA1 receptor agonist 8-OH-DPAT (8-Hydroxy-2-(Di-n-propylamino) tetralin) has a remarkably similar behavioral outcome as quinpirole when administered chronically. In a spontaneous-alteration model, rats treated with 8-OH-DPAT exhibit perseverative behavior and indecisiveness in decision-making (Yadin, Friedman, & Bridger, 1991). Though, its neurochemical properties are quite different from those of quinpirole. Supporting the notion that the induction of compulsive behavior by both drugs is mediated by different mechanisms, quinpirole and 8-OH-DPAT do not cross-sensitize in effects (Alkhatib et al., 2013).

The stereotypic behavior of 8-OH-DPAT-treated rodents (serotonin syndrome like, forepaw treading and hypothermia) is driven not only by its binding to postsynaptic 5-HTA1 receptors, but 5-HT1A is also a major serotonin autoreceptor working as a negative feedback system for the entire 5-HT system. The binding to presynaptic 5-HT1A receptors inhibits cell firing and decreases serotonin transmission (Hjorth et al., 1982). The concentration of 5-hydroxyindoleacetic acid (5-HIAA) was decreased after 8-OH-DPAT injection, suggesting a lowered turnover of 5-HT due to agonizing the presynaptic cell body receptors (Larsson, Unyi, Svensson, & Angeby-moller, 1990). Another observation supporting this is increased food intake in low-dose 8-OH-DPAT-treated animals (Dourish, Hutson, & Curzon, 1985), and hypothermia (Goodwin, De Souza, Green, & Heal, 1987). 8-OH-DPAT enhances the firing rate of mesolimbic dopaminergic neurons, the substrates of reward, and motivational behavior (Arborelius et al., 1993). Consequently, the repetitive stereotypical behavior seen in 8-OH-DPAT-sensitized rats in an open-field arena can be mediated by inhibiting effects on a serotonergic-negative feedback loop that normally decreases the dopaminergic drive created by the dangerous open-field exposure. Thus, It may keep serotonin positively affecting the dopaminergic activity by acting both on 5HT1A autoreceptors

and postsynaptic receptors and maintain the motivational state active (Alkhatib et al., 2013).

The 5-HT1A is a $G_{i/o}$-protein coupled receptor, and it has many intracellular cascades that mediate its action. Beyond the main function, i.e., inhibiting AC (adenylate cyclase) and decreasing the function of PKA (protein kinase A), it targets many different enzymes, kinases or channels to modulate various second messenger pathways, e.g., PLC (phospholipase C), NOS (nitric oxide synthase), MAPKs (mitogen-activated protein kinases), and many more. In the hippocampus, 8-OH-DPAT induced a decrease in PKA activity and training-induced CAMKII, which was accompanied by cognitive deficits (Fig. 5) (Chilmonczyk, Bojarski, Pilc, & Sylte, 2015).

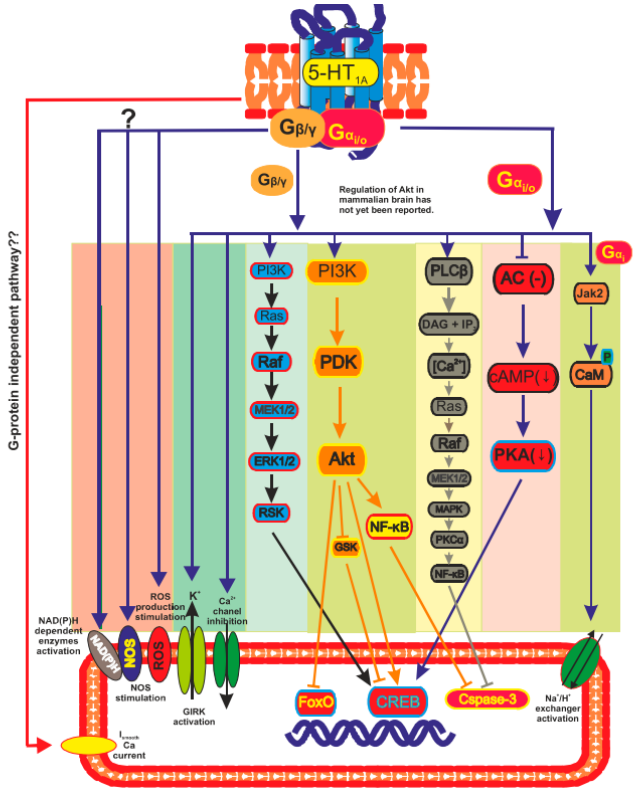


Figure 5: 5-HT$_{1A}$ receptor pathway *(Chilmonczyk et al., 2015).*

Activation of 5-HT1A by 8-OH-DPAT initiates phosphorylation of PKCδ (protein kinase c δ), which plays a role in proliferation, inflammation, and tumorigenesis by PKCδ-dependent activation of p47phox, a subunit of NADPH oxidase responsible for creating ROS (reactive oxygen species). Thus, initiating oxidative stress and inflammation could be one of the mechanisms behind serotonin syndrome and serotonin-induced behavior (Tran et al., 2019).

In a T-maze, 8-OH-DPAT administered rats show perseverative behavior. Instead of spontaneously altering the visited arms, as observed in control animals, they tend to pick only one, mirroring some aspect of the perseverative behavior in OCD patients (Odland, Jessen, Fitzpatrick, & Andreasen, 2019). Clomipramine and fluoxetine, but not desipramine, does prevent this behavior, supporting predictive validity (Fernández-Guasti, Ulloa, & Nicolini, 2003). However, it is not clear whether that is a naturally occurring homeostatic mechanism, where high extracellular 5-HT levels are downregulating 5-HT receptors, due to chronic blocking of 5-HT reuptake (Zike, Xu, Hong, & Veenstra-Van Der Weele, 2017). Therefore, there is still a problem with validating this model.

2.5.13 Optogenetic models

The optogenetic method is based on generating transgenic mice with cell populations reactive to light. Opsin (bacteriorhodopsin, halorhodopsin, or channelrhodopsin) transduction to specific cells with a virus vector into Cre-recombinase-expressing cells creates transgenic cells with membrane molecules that can be activated by light (Deisseroth, 2011). Optogenetically induced hyperactivity in the OFC-ventromedial striatum (VMS) pathway in mice is related to findings of hyperactivity in those areas in OCD patients as reviewed above. Acute stimulation of neurons in the OFC led to increased locomotion, decreasing immediately after turning the light off. Nevertheless, chronically stimulating mice for 5 minutes a day for two

weeks has triggered excessive grooming, observable even 24 hours after the light stimulus and were observable for two weeks afterward without any daily stimulation. This indicates an involvement of plasticity of the circuit, in this case, the OFC-VMS pathway, in generating OCD symptoms (in this case perhaps the fear of contamination) and that the circuit alteration may result from small bouts of hyperactivity in certain pathways. Chronic administration of fluoxetine successfully alleviated this grooming behavior in mice (Ahmari et al., 2013). The DBS stimulation, used for OCD treatment, works just contrarily to what was shown in the mentioned optogenetic study. The stimulation inhibits the OFC-VMS pathway by short bursts (De Koning, Figee, Van Den Munckhof, Schuurman, & Denys, 2011), giving this and other optogenetic models another piece of support as a new effective way for animal model development.

2.5.14 Endocrine models

Another animal model of OCD has been based on the intracerebral application of oxytocin. Oxytocin, a neuro-hypophyseal hormone that influences maternal behavior, bonding, grooming behavior, and anxiety (Myers et al., 2014), was injected into the amygdala of rats. This manipulation increased grooming behavior. In humans, grooming behavior is often an OCD symptom and it can occur in life in reproductive hormonal-cycles. Administration of estradiol to female rats attenuated lever-pressing behavior in a signal-attenuation model, although, after withdrawal from chronic administration of estradiol, rats have begun to lever-press even more, which can mimic the postpartum onset of OCD (Flaisher-Grinberg et al., 2009).

2.6 Cognitive flexibility

Cognitive flexibility is disrupted in OCD patients. Cognitive flexibility is a term describing the ability to change behavior or produce a variety of behaviors corresponding to a given, sometimes changed situation. All living organisms have this

ability to adapt and perceive situations from different perspectives to provide safety or reward (Banich, 2004). In mammals, such behaviors are mediated by the PFC, including infralimbic PFC, which is responsible for habitual/reward seeking. Recently, the role of hippocampal formation has been researched in this topic, because of its plasticity and critical role in decision-making and reward-seeking processes (Anacker & Hen, 2017).

2.6.1 Cognitive flexibility assessments in humans

Cognitive flexibility in humans can be assessed by many different tasks, nevertheless, the most used in diagnostics are the Wisconsin Card Sorting Test (WCST) and Cambridge Neuropsychological Test Automated Battery (CANTAB), in which they divided the discrimination tasks into intra-dimensional set-shifting (ID) and extra-dimensional set-shifting (ED). The WCST consists of a set of cards that are sorted based on a cue that changes unannounced. Increased perseveration was reported in OCD vs. healthy controls, which correlated with the Y-BOCS score (Lucey et al., 1997). CANTAB works with a test of cards as well. ID changes the specifics of the rule, but the rule remains the same (f.e. color changes from blue to green). ED changes the rule (f. e. shape is now the discrimination characteristic instead of color) (Sahakian & Owen, 1992). Both ID and ED performance is significantly deficient in OCD (Snyder, Kaiser, Warren, & Heller, 2015).

I will briefly summarize some other tasks as well. In Object Alternation Task (OAT), subjects choose one object out of two or more. They are rewarded, for choosing different objects each time. OCD patients tend to be more perseverative and less successful in this task. In reversal learning, reward comes after a specific cue that changes without saying to the subject (however less complex than ID/ED tasks). This task measures the capability to adjust stimulus-reward behavior. Differences in brain activity of OCD patients and healthy controls were measured, however with no significant behavioral change. Performance in the Stroop test is also deficient in OCD

patients. This test of cognitive inhibition consists of the written name of colors in a distinct color. Subjects are instructed to name the color in which the name is printed (Fig. 6) (Snyder et al., 2015). There are many other tests for cognitive flexibility predominantly supporting cognitive inflexibility in OCD (Gruner & Pittenger, 2017).

Figure 6: The Stroop test example *(Adapted from Jensen & Rohwer, 1966).*

2.6.2 Cognitive flexibility assessment in animals

To evaluate flexibility on animals, behaviors such as reversal learning, and models of ID and ED can be used. This can be assessed in a T-maze, or more precisely a carousel maze with reversal (Hatalova, Radostova, Pistikova, Vales, & Stuchlik, 2014). In a quinpirole animal model of OCD (reviewed in chapter 2.4.) cognitive flexibility is impaired (Hatalova et al., 2014) and alleviated by co-treatment with clomipramine and risperidone (Hatalova, Radostova, Pistikova, Vales, & Stuchlik, 2017). Cognitive functions in this study were assessed in an active place avoidance with reversal on a Carousel maze and in a two-way active avoidance task in shuttle boxes. Quinpirole binding to the D2 receptor can change hippocampal flexibility and, in this way, cause cognitive deficiency seen in these animals (Hatalova et al., 2017). Another

rodent model of cognitive flexibility impairment is a microinfusion with tetracaine hydrochloride into the pre-limbic and infralimbic areas (Ragozzino, Detrick, & Kesner, 1999), or inactivation of the NAc by GABA agonists baclofen or muscimol (Floresco, Ghods-Sharifi, Vexelman, & Magyar, 2006).

2.7 Learning and memory

Memory has been implicated to have a key role in the OCD symptoms. Questioning themselves and their actions, it seems that some patients fail to store eloquent information (Christensen et al., 1992) or lack of confidence in their memory (Constans, Foa, Franklin, & Mathews, 1995). For example, they are often unsure whether they performed an action, such as closing the door or washing their hands. Thus, the most relevant form of memory involved in OCD behavior is episodic memory, the remembrance of personal events. Episodic memory can be divided into verbal memory and nonverbal memory (Muller & Roberts, 2005). OCD patients score poorly on verbal memory tasks, mainly when they are time-related (Christensen et al., 1992). Patients with OCD had lower scores also in spatial working memory, spatial recognition, and motor initiation and execution as well (Purcell, Maruff, Kyrios, & Pantelis, 1998). Another study found that OCD patients tend to focus more on irrelevant details and less to the important (Rauch et al., 1997). Substantially, it seems that they have a memory bias for negative threat-related information (Tolin, Hamlin, & Foa, 2002). A general impairment in discrimination learning was observed in adolescents with OCD (Gottwald et al., 2018). In a recent meta-analysis study of OCD patients and their relatives, congruent results showing inhibition, planning, and decision-making deficits were found in those two groups, however, OCD patients scored much lower in all of them and had more cognitive deficits in visual memory and set-shifting task (Bora, 2020). This suggests that a memory deficit could constitute an endophenotype of OCD. Overall, there is a consistency in visuospatial memory dysfunction in patients

with OCD. However, it is not entirely clear yet, whether it is due to a deficit in the organization of information or memory itself (Kuelz, Hohagen, & Voderholzer, 2004).

2.7.1.1 Learning and memory assessment in humans

For nonverbal memory, the most used test is the Rey Osterrieth Complex Figure Test (RCFT). In The RCFT, participants are asked to reproduce a geometrical drawing and then to draw it again from memory. Immediate recall is after 3 minutes of the reproduction, delayed recall after 30 minutes. Additionally, the Benton Visual Retention Test (BVRT) is used, in which the participant retrieves ten previously shown designs.

Verbal working memory is usually assessed by the WAIS-R Digit Span task. Participants repeat a sequence of digits previously heard or read. The number of digits increases after each trial. The participant can be asked to repeat the numbers forward, or backward. The Rey Auditory Verbal Learning Test measures short-term verbal memory, learning rate, and strategy. Participants repeat (immediately and then after 30 minutes again) words that have been presented five times before (Kuelz et al., 2004). The Logical Memory (LM) subtest of the Wechsler Memory Scale (WMS-LM) assesses auditory memory. Participants in the WMS-LM recall a story that was presented to them (Abikoff et al., 1987).

2.7.1.2 Learning and memory assessments in animal models

In animals, episodic-like memory can be measured by several distinct procedures. One of them is a radial arm maze, where some of the arms contain regular pellets, some nothing, and one chocolate pellet. The chocolate pellet is always given to the same arm, however, not after each trial, with short and long intervals between. The rats were able to remember what food and where they found and when there was the chocolate, giving it a good validity for future research (Crystal, 2009). Object recognition is a procedure where rats are presented with two objects, later on, test day,

one of the objects is replaced with a new one. Because the rats are spontaneously preferring the novel object, the recognition of the familiar object is perceived as successful when the rat spent more time with the novel object (Lueptow, 2017).

Place avoidance tasks are used for the evaluation of spatial learning or memory deficit. In passive avoidance in general, an unpleasant event will inhibit the behavior that led to it. In an active avoidance, the animal must prevent an unpleasant event by producing a specific behavior. The spatial version of avoidance tasks (Bures, Fenton, Kaminsky, & Zinyuk, 1997) is usually performed by a Carousel maze with a "to-be-avoided" sector, where the animal gets a mild footshock upon entering the sector. In the passive place avoidance task, rats were trained on a stable arena, on which a stable "to-be-avoided" sector was defined. Animals in this task learn the position of the sector very quickly, long-term memory storage is observable after three days (Cimadevilla, Kaminsky, Fenton, & Bures, 2000). In active place avoidance, animals must avoid the stable sector in a rotating arena. This task then taxes the animal's capability to relate to external marks, creating a strategic active task. Working memory is acquired when the "to-be-avoided" sector is changed every day (Zemanova et al., 2013). Reference memory (required for long term memory) is acquired by keeping the sector in one place (Cimadevilla et al., 2000). Beside spatial avoidance learning, the task can be also used to study cognitive coordination (Wesierska, Dockery, & Fenton, 2005), the ability to segregate spatial information from the arena and room into coherent subsets and select the room frame as relevant for navigation (Kubík & Fenton, 2005).

3 Aims of the study and experimental hypotheses

Memantine and riluzole have been used off-label for the treatment of various neuropsychiatric disorders, including OCD. Therefore, we sought to determine the effects of these two drugs on the rat model of cognitive dysfunction in OCD tested in the active place avoidance task and induced by chronic intermittent application of 5-HT1A receptor agonist 8-OH-DPAT.

The specific hypotheses were the following:

1) Sensitization of 5-HT1A receptors with specific agonist 8-OH-DPAT impairs place learning measured by the acquisition of the active place avoidance task in the Carousel maze.

2) Acute systemic administration of memantine and riluzole before the acquisition testing alleviates the deficit induced by sensitization with 8-OH-DPAT in:

    a. Rats sensitized by 8-OH-DPAT, but not treated with 8-OH-DPAT during the acquisition testing.
    b. Rats sensitized with 8-OH-DPAT and treated with this drug during the acquisition testing.

4 Methods

4.1 Animals

Ninety-six male adult Long-Evans rats at the age of 3-5 months were obtained from a breeding colony of the Institute of Physiology of the Czech Academy of Sciences were used. The breeding core was obtained from Charles River (Italy) but rats were bred for multiple generations at the Institute. Their body weight was 300-500 g at the start of the experiments. Animals were housed in groups of 2-4 in transparent plastic cages (25 x 30 x 20 cm) in an accredited animal room with a 12/12 h light/dark cycle. The air-conditioned animal room had a stable temperature and humidity. Water and food were freely available throughout the experiments. Animals were assigned pseudorandomly to groups and they were handled for 3 minutes daily for 5 days before the experiment. The behavioral testing was conducted in the light phase of the day. All manipulations with animals were done per the Animal Protection Code of the Czech Republic and a corresponding directive of the European Community Council on the use of laboratory animals (2010/63/EC). They were approved by the local and central (Ministry of Agriculture) animal care committees (Project of Experiments No. 50/2016).

4.2 Drugs and design

8-OH-DPAT was purchased from Sigma-Aldrich, Czech Republic, Cat. No. H8520 and dissolved in isotonic saline (0,9% sodium chloride in distilled water) at a concentration 0.25 mg/ml. Memantine hydrochloride (Mem, Sigma-Aldrich, Czech Republic, Cat. No. M9292) and riluzole (Sigma-Aldrich, Czech Republic, Cat. No. R116) were diluted in saline to 1 mg/ml and subcutaneously injected (1 mg/kg) 30 minutes before 8-OH-DPAT/saline injections and behavioral testing in Carousel maze. All injection volumes were 1 ml/kg of body weight. A fresh solution was prepared before each trial.

The experiment had habituation (Fig. 8) and an acquisition phase (Fig. 10). The habituation phase included 5 days of handling, followed by 3 days of handling with habituation to injection (subcutaneous injection with isotonic saline – 1 ml/kg) and subsequently, 8 sessions every other day in the apparatus for 50 min, during which animals were sensitized by OH-DPAT (and controls treated with saline. Immediately before being put into the apparatus, the rats were injected subcutaneously with 0.25 mg/kg 8-OH-DPAT (N=84) dissolved in saline or saline solution (N=14). During the acquisition phase, rats were applied with two injections (memantine, riluzole, or saline 30 min before the test and 8-OH-DPAT or saline immediately before the test).

During the acquisition phase, rats treated with saline during the habituation served as a global control group (N = 14; **Global Controls**) and obtained two injections of saline before acquisition as controls for OH DPAT and memantine or riluzole. Rats sensitized to 8-OH-DPAT (N = 84) previously during habituation were pseudorandomly assigned into six subgroups according to their treatment regime during acquisition: saline control group (0.9% NaCl, Sal-Sal, N=14; **Sensitized/Undrugged/Untreated**), 8-OH-DPAT control group (Sal-OH, N=14 (**Sensitized/Drugged/Untreated)**), group that received memantine and then 8-OH-DPAT (Mem-OH, N=14; **Sensitized/Drugged/Treated**), memantine and then saline (Mem-Sal, N=14; **Sensitized/Undrugged/Mem-Treated**), group that received riluzole and then 8-OH-DPAT (Ril-OH, N=14; **Sensitized/Drugged/Ril-Treated**), and riluzole and saline (Ril-Sal, N=14; **Sensitized/Undrugged/Ril-Treated**). The acquisition phase had 10 sessions and it proceeded every other day. Corresponding groups were compared during the analysis. That is: The Sensitized/Drugged/Untreated served as a control for Sensitized/Undrugged/Mem-Treated, and for Sensitized/Drugged/Ril-Treated). Similarly Sensitized/Undrugged/Untreated served as a control group for Sensitized/Undrugged/Mem-Treated, and Sensitized/Undrugged/Ril-Treated (Fig. 7).

Habituation	N	Acquisition	Acquisition	N	Description
1 injection before the test		1st injection (30 min before the test)	2nd injection (before the test)		
Saline	N=14	Saline	Saline	N=14	Global controls
8-OH-DPAT	N=84	Saline	Saline	N=14	Sensitized/Undrugged/Untreated
8-OH-DPAT		Memantine	Saline	N=14	Sensitized/Undrugged/Mem-treated
8-OH-DPAT		Riluzole	Saline	N=14	Sensitized/Undrugged/Ril-treated
8-OH-DPAT		Saline	8-OH-DPAT	N=14	Sensitized/Drugged/Untreated
8-OH-DPAT		Memantine	8-OH-DPAT	N=14	Sensitized/Drugged/Mem-treated
8-OH-DPAT		Riluzole	8-OH-DPAT	N=14	Sensitized/Drugged/Ril-treated

Figure 7: The design of the treatment plan

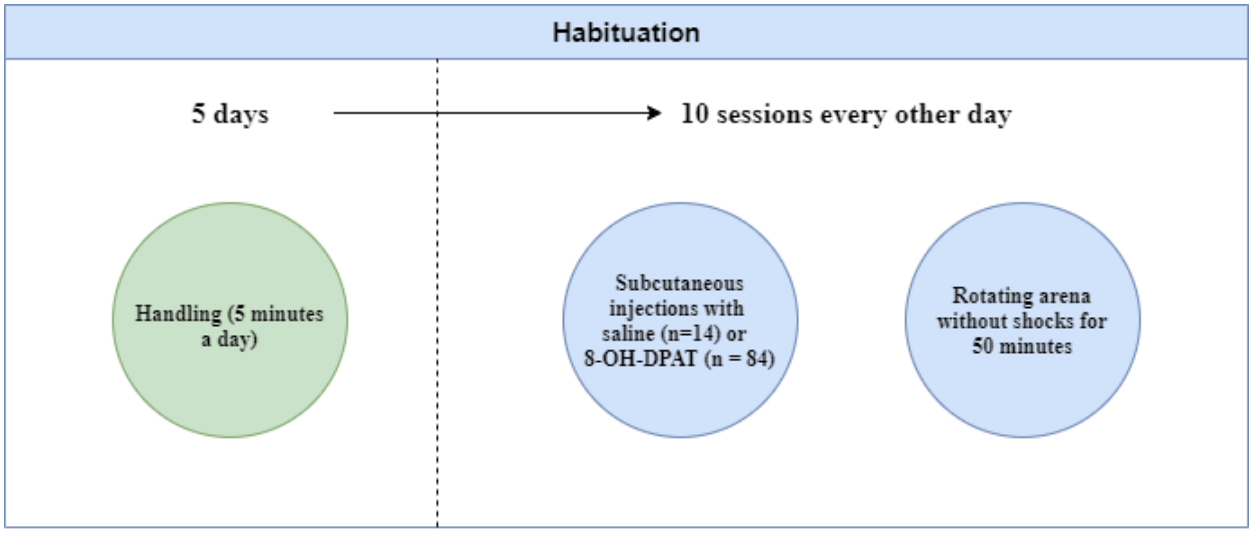


Figure 8: The design of the habituation phase

4.3 Apparatus and behavioral procedure

4.3.1 Carousel maze

All experiments were done on a rotating arena – the Carousel maze (Bures et al., 1997; Stuchlík et al., 2013). The apparatus was a smooth metallic disk of a circular shape (diameter of 82 cm) enclosed by a 60-cm-high acrylic transparent wall in the conical shape (to prevent reflections to the camera). The arena was elevated 1m above the floor of experimental rooms containing an abundance of visual extra-maze landmarks. The arena rotated clockwise at a velocity of 1 revolution per min and an unmarked "to-be-avoided" sector (60 degrees) was defined on it in room-frame coordinates, thus, it did not move with the arena. The animal walked on the arena and had an infrared light-emitting diode (LED) mounted on s small and light rubber jacket on the back. This LED was used to monitor the locomotion of the rat by a camera above the arena. The apparatus was operated by the computer software Tracker (Biosignal Group, USA). Upon entering the "to-be-avoided" sector, the tracking system delivered a mild electric shock (AC, 50 Hz; 0.2 mA – 0.6 mA) through a subcutaneous needle implanted between rat´s shoulders to the grounded arena floor (Fig. 9). Offline analysis programs TrackAnalysis (BioSignal Group, USA) and Carousel Maze Manager (CMM; Bahnik, 2017) were used to analyze the trajectories offline and extract the evaluated parameters.

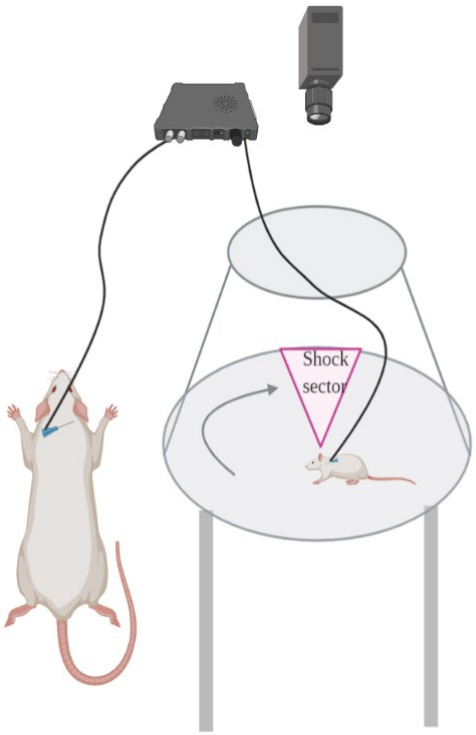


Figure 9: Scheme of the Carousel maze apparatus and shock mechanism

4.3.2 8-OH-DPAT sensitization and habituation

The sensitization to 8-OH-DPAT was done in the habituation phase. This provided the chronic model. The rats were injected with 8-OH-DPAT at a dose of 0.25 mg/kg or saline at a volume of 1 ml/kg every other day a total of 8 injections. Immediately after the injection, the rats were put into the Carousel maze for 50 minutes. The arena was rotating but there were no shocks in the habituation phase, so the rats could explore and habituate to the rotating arena.

4.3.3 Acquisition testing

Before the acquisition, the animals were implanted with a subcutaneous needle between their shoulders, which was in the acquisition phase used for connecting to a source for the electric shocks. The animals were tested every other day with a total of 10 days/10 injections. 30 minutes before each trial, rats were injected with riluzole or memantine (both 1mg/kg) or saline. Immediately before the arena, rats were injected with saline again or with 8-OH-DPAT (0.25mg/kg). Afterward, they were placed into the maze to the side opposite to the “to-be-avoided” sector. The arena rotated for the whole 50 minutes of the trial and had no cues inside, so the animals had to learn to use external landmarks to avoid the shock sector (Fig. 10).

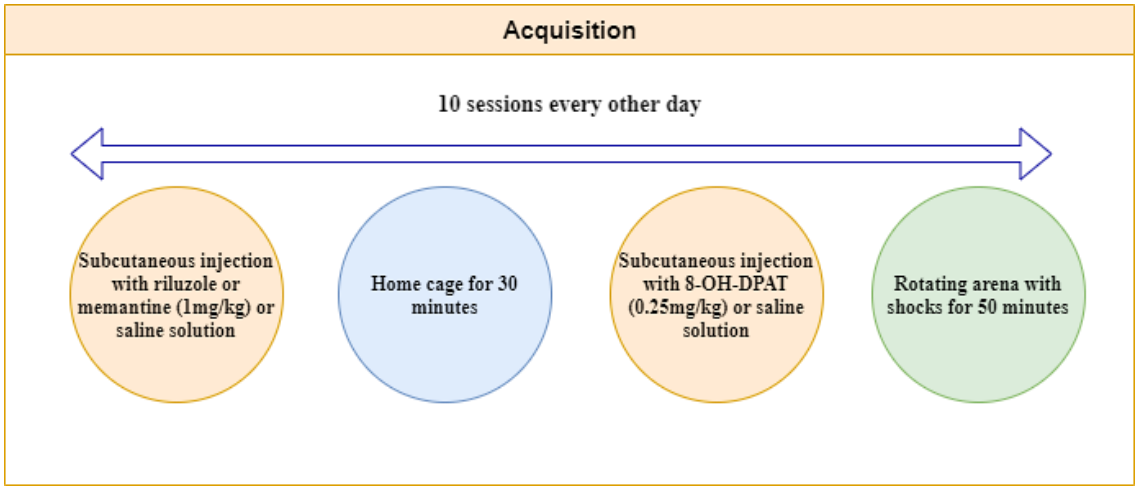


Figure 10: The design of the acquisition phase

4.4 Measured parameters, data analysis, and statistics

The parameters selected for the statistical evaluation were: the total distance, number of entrances into the shock sector, number of shocks received (the apparatus gives the rat a shock every 1800 ms until the animal leaves the sector), and median speed after shock. The total distance measures the locomotor activity (spontaneous locomotion during habituation with no shock, and rotation-forced locomotion during the training with shocks) and the number entrances into the to-be-avoided sector is the most used parameter of the efficiency of avoidance learning as an error count (Stuchlík et al., 2013). Median speed after shock and the total number of shocks are measures of the efficiency of escape reaction upon entering the sector and getting the first shock. More specifically, the number of shocks is a combined parameter of learning and escape efficiency with a variable contribution of both factors depending on the number of additional shocks after the first one, and median speed after shock is a measure of a startle-like episode of running after the shock, not reflecting the actual efficacy of escape, i.e. whether the rat escaped to a safe place.

The parameters for the whole session, as well as five consecutive 10-minutes intervals from each session, were analyzed. The statistical analysis was done by a three-

way ANOVA with repeated measures (session x interval x treatment) and Greenhouse-Geisser correction. Games-Howell post hoc tests were used when applicable. Homogeneity of variances was measured by Levene's test and normality of distribution by the Shapiro-Wilk test. For data without normal distribution, logarithmic transformation was used. Statistical analysis was done in SPSS software (SPSS Inc. Released 2019. SPSS Statistics for Windows, Version 26.0. Chicago: SPSS Inc.). Transformed data is shown in the graphs without error bars (for simplicity) except the graph 1, however, means of all parameters for the final session are shown in the text and means ± standard errors of the mean (S.E.M.) are summarized in the table at the end of Results section to get a grasp of the original values (Fig. 13).

5 Results

5.1 The analysis of habituation to the arena and sensitization to 8-OH-DPAT

As can be seen from the trajectories (Fig. 11, bottom panels), the 8-OH-DPAT-treated ratwas less mobile in the beginning and after several minutes started to be hyperlocomotive. On the contrary, the control group begins the session on the 10th day walking in the arena, but after 10-20 minutes sat down and was immobile till the end of the session.

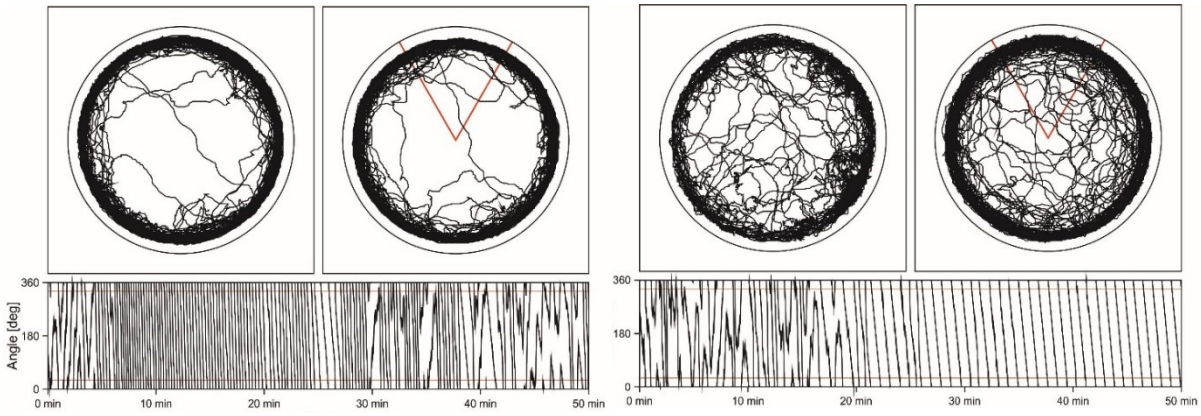
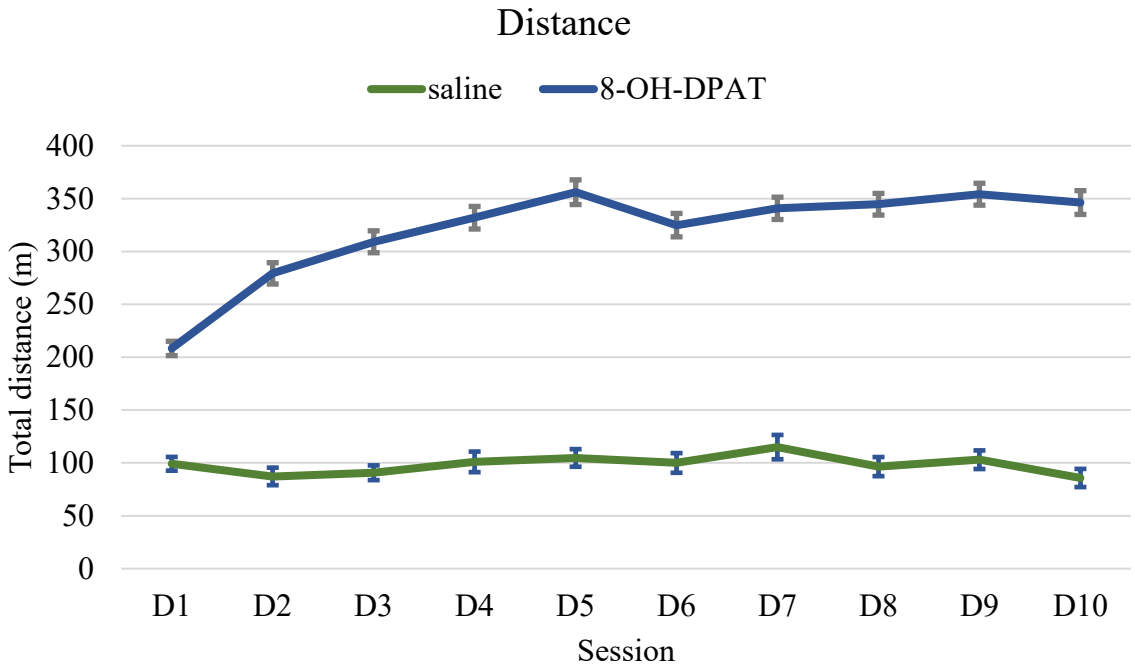


Figure 11: Trajectories from the 10th habituation session. *8-OH-DPAT group on the left, control group (saline) on the right. On the upper left side is arena-frame (how the animal moved in the arena context) and on the right side a room-frame (how the animal moved in the room context). The "to-be-avoided" sector is marked red. The graph below is showing the trajectory in a linear manner with the angle towards the "to-be-avoided" sector, X-axis – time, Y-axis – angle towards the "to-be-avoided" sector.*

The sensitization to 8-OH-DPAT during habituation markedly increased locomotion (graph 1) [$F(1, 85) = 90.580$, $p < 0.001$]. The data met the assumption of normality, but not sphericity, thus repeated-measure (RM) ANOVA with Greenhouse-Geisser correction was used. The mean distance for rats that received 8-OH-DPAT on day 10 was 346 m, for the saline group 86 m. This result replicated the previous findings of hyperlocomotion after 8-OH-DPAT sensitization.



Graph 1: The comparison of the total distance traveled (mean ± S.E.M.) during habituation on 8-OH-DPAT and saline*. Animals receiving 8-OH-DPAT had significantly higher locomotion in all sessions compared to the saline control group. X-axis – daily sessions, Y-axis – Total distance (m).*

5.2 The analysis of total distance during acquisition

Animals that received 8-OH-DPAT were more locomotive during the 10th day of acquisition. As seen in figure 12, Sensitized/Drugged/Untreated animals did not avoid the shock sector and the Sensitized/Drugged/Mem-treated and Sensitized/Drugged/Ril-treated groups were even more locomotive and received more shocks. The Sensitized/Drugged/Ril-treated group was the most locomotive. Both control groups (Global control and Sensitized/Undrugged/Untreated) and Sensitized/Undrugged/ Mem-treated or Ril-treated moved in the arena only for the sake of avoiding the shock sector.

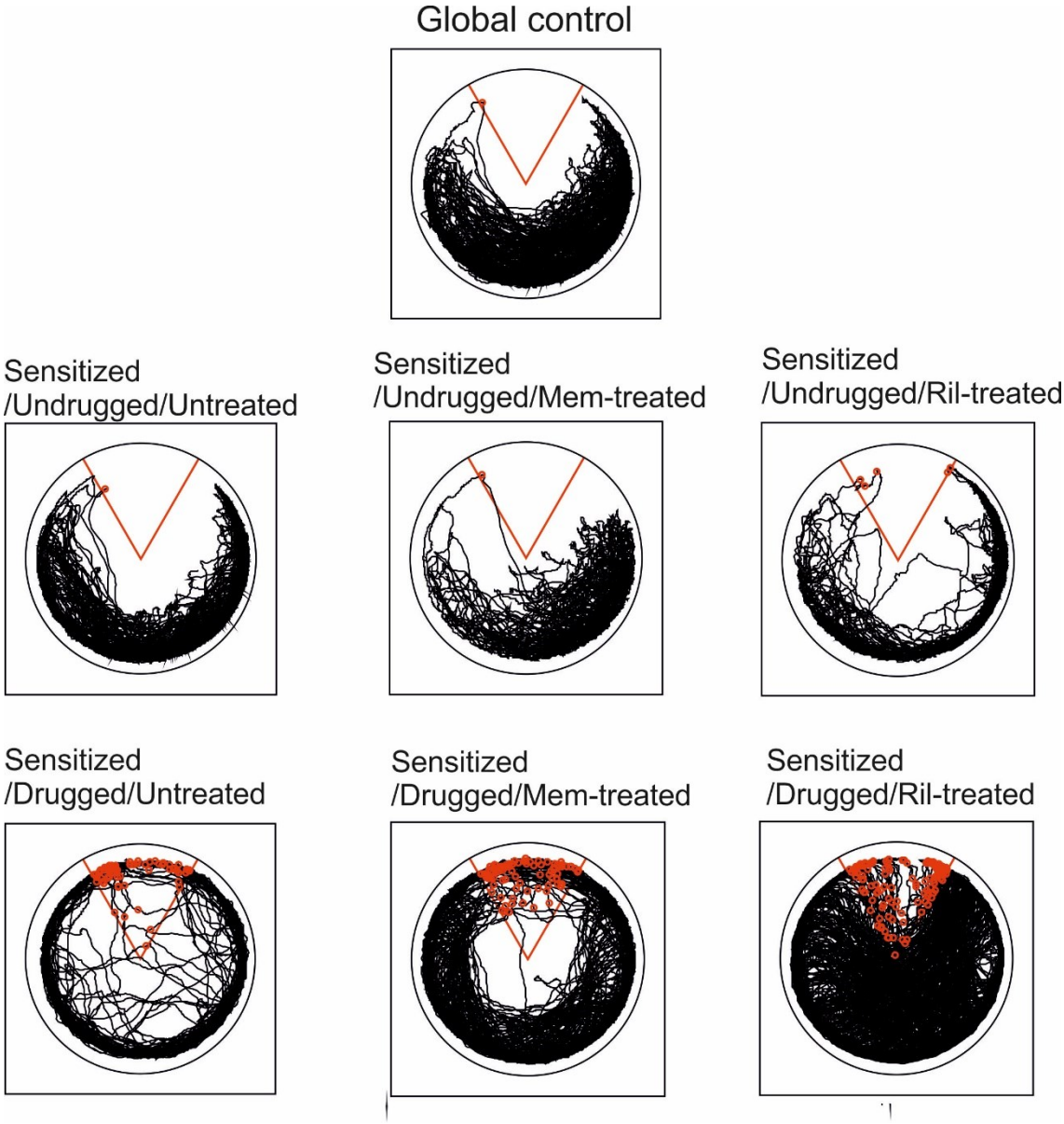
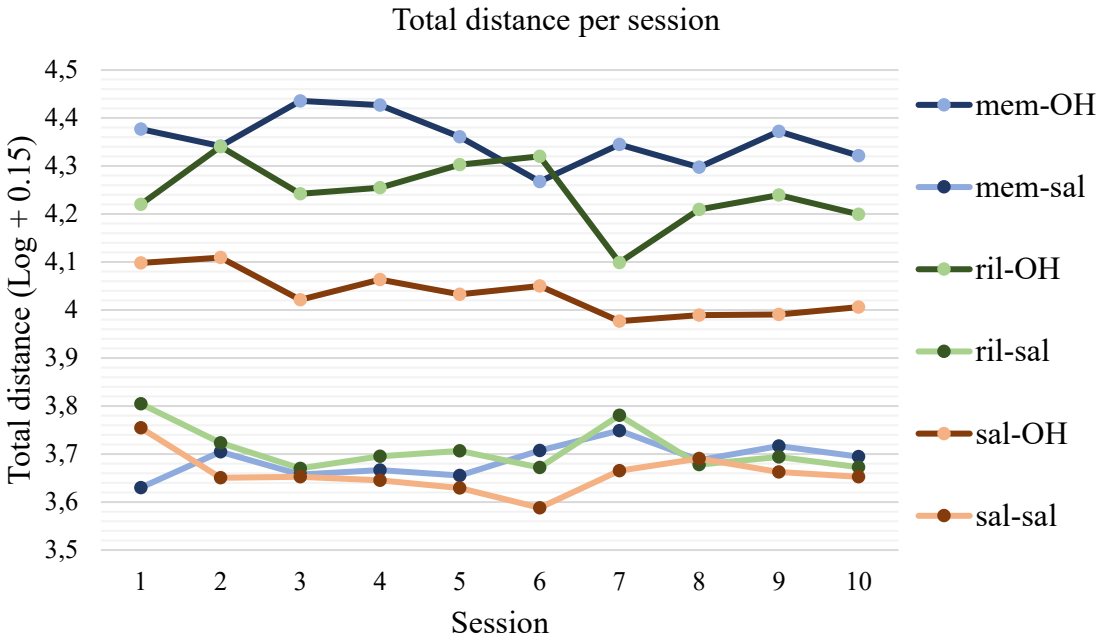
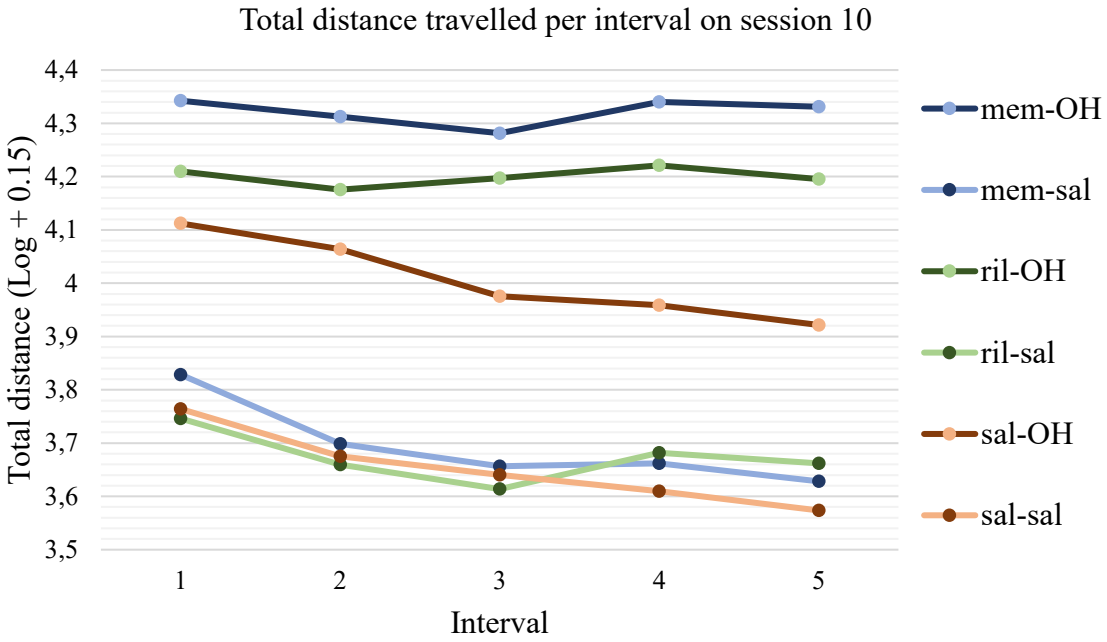


Figure 12: The trajectories of all groups during the 10th session of acquisition in a room-frame. *The "to-be-avoided" sector is marked in red and shocks received are marked as red circles. Global controls and Sensitized/Undrugged/Untreated avoided the sector well, as well as the Sensitized/Undrugged/Mem-or-Ril-treated groups. All groups that received 8-OH-DPAT also during acquisition were more active and they did not avoid the shock sector efficiently.*

The data were not normally distributed; therefore, RM ANOVA was conducted on data transformed by log + 0.15. Assumption of sphericity was not met; therefore, Greenhouse-Geisser correction was used. The analysis showed the main effect of interval [$F(1.912, 166{,}340) = 27.894$, $p < 0.001$], day (session) x interval [$F(16.991, 1478.241) = 3.032$, $p < 0.001$] and interval x treatment interaction [$F(9.560, 166{,}340) = 2.555$, $p = 0.008$]. However, Games-Howell post hoc test revealed that OH-DPAT groups (Mean on session 10: Mem-OH = 353 m, Ril-OH = 318 m, Sal-OH = 275 m) significantly differed only from saline groups (Mean on session 10: Mem-Sal = 178 m, Ril-Sal = 165 m, Sal-Sal = 162m) (graph 4 and figure 11). The Memantine-OH group and the riluzole-OH group did not significantly differ from the saline-OH group. Therefore, neither memantine nor riluzole alleviated the hyperlocomotion induced by OH-DPAT. Contrarily, animals that received OH-DPAT together with memantine and riluzole were even more active than the group that received OH-DPAT together with saline (graph 2). As can be seen in graph 4, the animals that received 8-OH-DPAT were hyperactive even on the day (session) 10, and the only saline-8-OH-DPAT group had slightly reduced its locomotion throughout the session, in contrast to saline groups (graph 3).



Graph 2: The comparison of the total distance traveled during the whole acquisition of all animal groups after transformation. *Animals that received 8-OH-DPAT (Sal-OH) had significantly higher locomotion then the saline groups (Mem-Sal, Ril-Sal, Sal-Sal) and riluzole and memantine exacerbated this effect even more (Mem-OH, Ril-OH). X-axis – daily sessions, Y-axis – Total distance (m; log+0.15).*

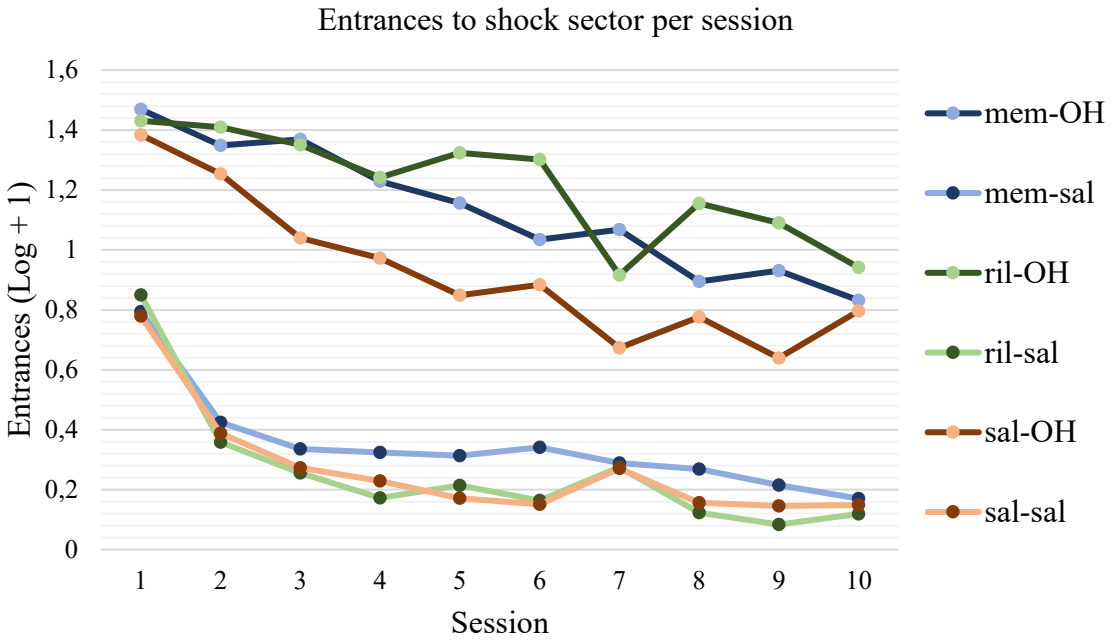


Graph 3: The comparison of total distance traveled at day (session) 10 per intervals after transformation. *Group Mem-OH was the most active, followed by Ril-OH and Sal-OH. Groups receiving saline instead of 8-OH-DPAT before the test had been significantly less active in all intervals, with the largest difference in interval 5 (40-50 min). X-axis – 10 min intervals, Y-axis – Total distance (m; log+0.15).*

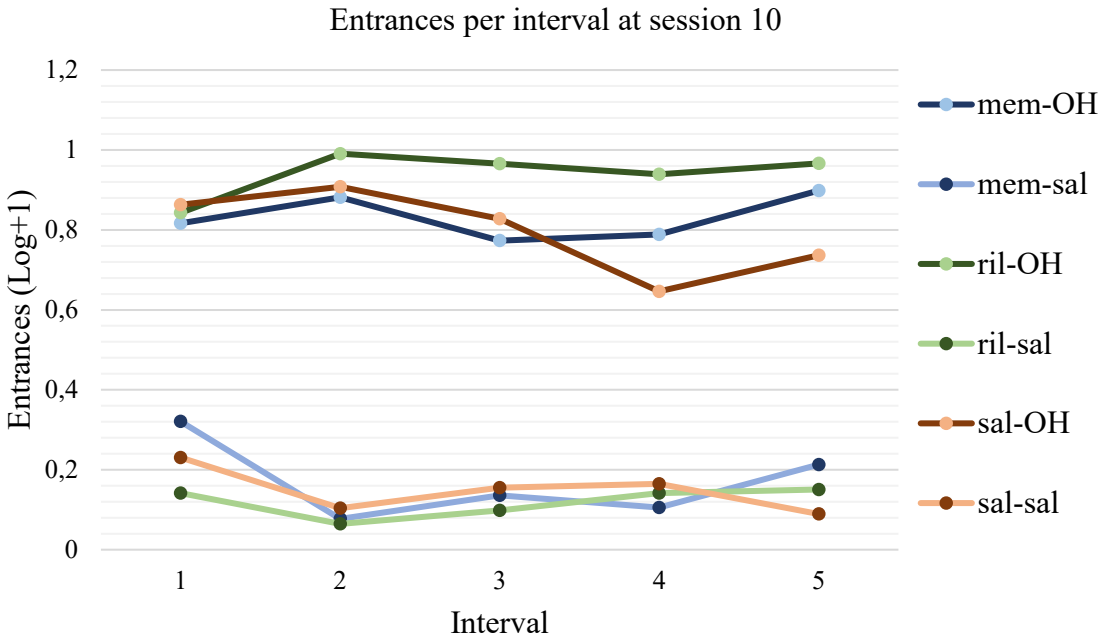
5.3 The analysis of the number of errors during acquisition

An entrance into the "to-be-avoided" sector is considered an error and it is the most straightforward parameter for the ability of learning. Since the data were not normally distributed, three-way RM ANOVA was conducted on data transformed by logarithm. Assumption of sphericity was not met, thus Greenhouse-Geisser correction was applied. Analysis showed the main effect of session [$F(4.009, 360.789) = 48.855$, $p < 0.001$], session x interval [$F(20.044, 360.789) = 2{,}163$, $p = 0.003$], interval [$F(1.881, 169.319) = 21.319$, $p < 0.001$], interval x treatment [$F(9.407, 169.319) = 2.163$, $p < 0.001$], session x interval [$F(21.489, 1934.002) = 5.259$, $p < 0.001$], and session x interval x treatment interaction [$F(107.445\ 1934.002) = 1.430$, $p = 0.003$]. Though, the

Games-Howell post hoc test uncovered that OH-DPAT groups (Mem-OH, Ril-OH, Sal-OH) significantly differed only from saline groups (Mem-Sal, Ril-Sal, Sal-Sal). The Mem-OH group and the Ril-OH group did not significantly differ from the saline-OH group. Again, neither riluzole nor memantine alleviated the number of errors increased by 8-OH-DPAT. Contrarily, animals that received 8-OH-DPAT and memantine or riluzole had worse performance than the group that received OH-DPAT together with saline (graph 4). To analyze the effect of session and session x treatment interaction simple planned contrasts were used. They revealed that all groups had a significantly higher number of entrances on the first six sessions compared to the last session ($p < 0.001$). The session x treatment interaction was significant in the fourth, fifth, and sixth sessions compared to the last session. As showed in graph 4, the number of entrances in saline groups decreased only slightly after the sixth session. On the other hand, the number of entrances in OH-DPAT groups decreased even after the sixth session. Regarding the intervals, there was a contrast in all intervals except for the third one. With interval x treatment interaction being the most visible in the first interval. Despite this constant improvement, OH-DPAT groups had a significantly higher number of entrances through the whole acquisition sessions (mean on session 10: Mem-OH = 77, Ril-OH = 99, Sal-OH = 69) compared to (mean on session 10: Mem-Sal = 3, Ril-Sal = 2, Sal-Sal = 2), which suggests impaired spatial learning (Fig. 13).



Graph 4: The number of entrances per session after transformation. *Groups that received 8-OH-DPAT had a significantly higher number of errors, suggesting impaired spatial learning. Riluzole and memantine aggravated this effect again. The animals were improving, however, the 8-OH-DPAT groups were significantly worse even on day 10. X-axis – Daily sessions, Y-axis – Entrances to shock sector (log+1).*

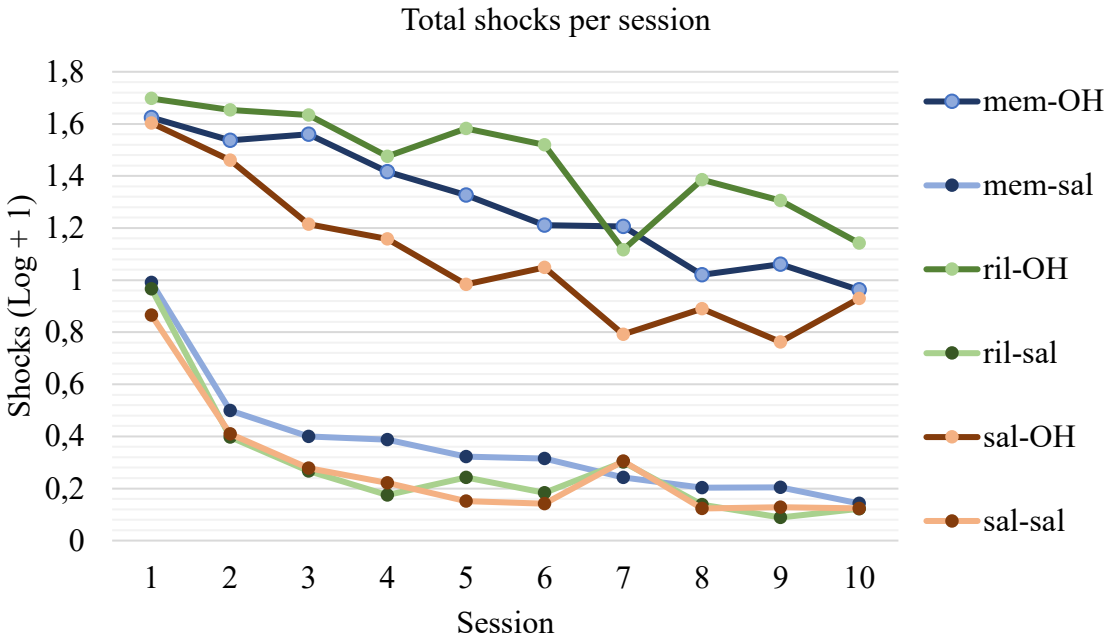


Graph 5: The number of entrances per interval at the 10th session after transformation. *Groups that received 8-OH-DPAT had a significantly higher number of entrances to the shock sector at the last session. The animals were not improving during the session. X-axis – 10-min intervals, Y-axis – Entrances to shock sector (log+1).*

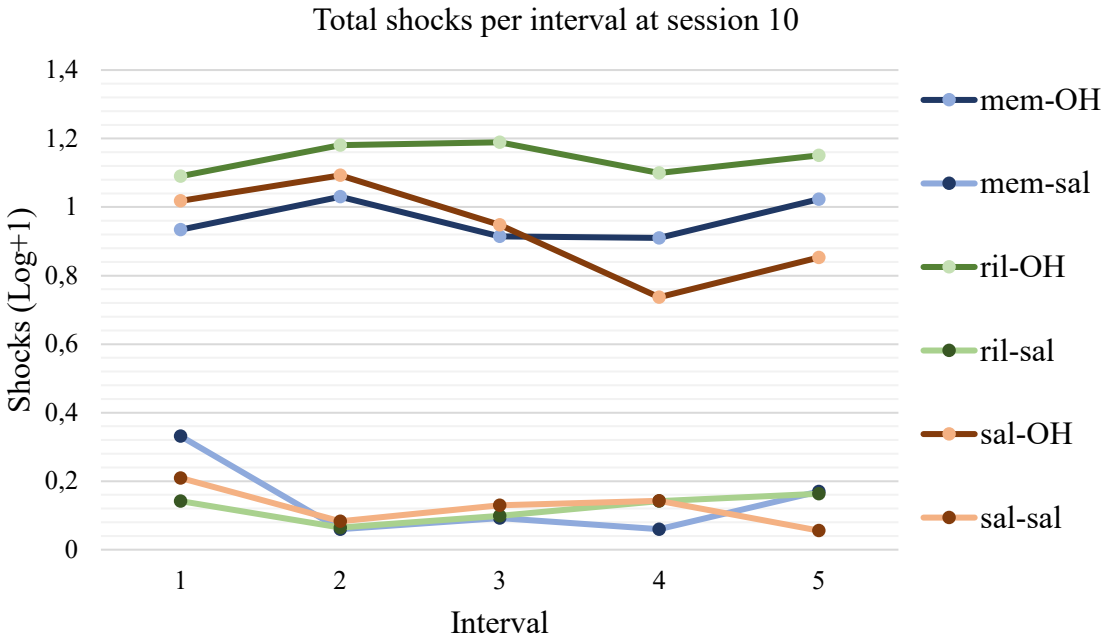
5.4 The analysis of the total shocks during acquisition

The number of shocks received is a combined parameter of learning to avoid and generate efficient escape reaction from the shock sector to a safe place. Upon error, the rat received the first shock, and the shocks were repeated at regular intervals until the animal escaped the sector. The results of this parameter confirmed that the 8-OH-DPAT groups were significantly worse than the saline groups, and riluzole and memantine increased the number of shocks received even compared to animals only sensitized and treated with 8-OH-DPAT. The actual shock counts were higher than the entrances count. However, given the hyperlocomotion and higher median speed after shock in the 8-OH-DPAT group (see the next section and graph 8), it suggests that all animals could

generate an efficient escape reaction. Nevertheless, they sometimes did not escape into the safe space but only to other locations within the sector. Means on session 10: Mem-OH = 133, Ril-OH = 161, Sal-OH = 115, Mem-Sal = 5, Ril-Sal = 2, Sal-Sal = 4 (Fig. 13). Data were logarithmically transformed, and three-way RM ANOVA was used. They showed main effect of all parameters, session [$F(3.955, 355.984) = 52.947$, $p < 0.001$], session x treatment [$F(19.777, 355.984) = 2.345$, $p < 0.001$], interval [$F(1.829, 164.575) = 24.594$, $p < 0.001$], interval x treatment [$F(9.143, 164.575) = 5.366$, $p < 0.001$], session x interval [$F(36, 1820.447) = 6.024$, $p < 0.001$], day x interval x treatment [$F(101.136, 1820.447) = 1.758$, $p < 0.001$]. In the Games-Howell post hoc test, only 8-OH-DPAT groups differed significantly from the saline groups. Simple planned contrast revealed that all groups significantly differed from the last session during the first six sessions. In sessions 3, 4, and 5, a significant difference in session x treatment interaction was shown, as can be seen in graph 6, saline groups were getting fewer shocks from session three and 8-OH-DPAT were getting fewer shocks since the sixth session. A significance in the interval main effect as well as in interval x treatment interaction manifested that 8-OH-DPAT groups were impaired relative to saline groups (graph 7).



Graph 6: The number of shocks per session after transformation. *Groups that received 8-OH-DPAT had a significantly higher number of total shocks received, suggesting impaired learning and escape response. Riluzole and memantine aggravated this effect. The animals were improving, however, the 8-OH-DPAT groups were significantly worse even on day 10. X-axis – Daily session, Y-axis – Total shocks (log+1).*

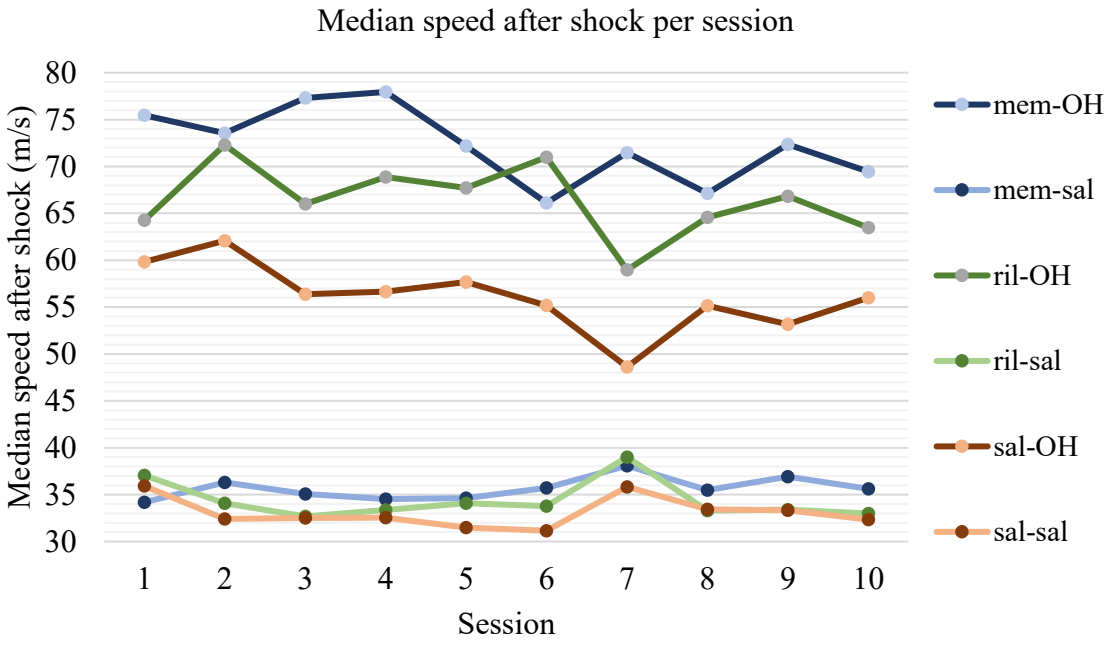


Graph 7: The number of shocks per interval on session 10 after transformation. *The 8-OH-DPAT groups did not learn to avoid the shock sector even in the 10th session. They did not learn to avoid the sector trough the session. The saline groups received a few shocks only in the first (0 – 10 min) interval. X-axis – 10-min intervals, Y-axis – Total shocks (log+1).*

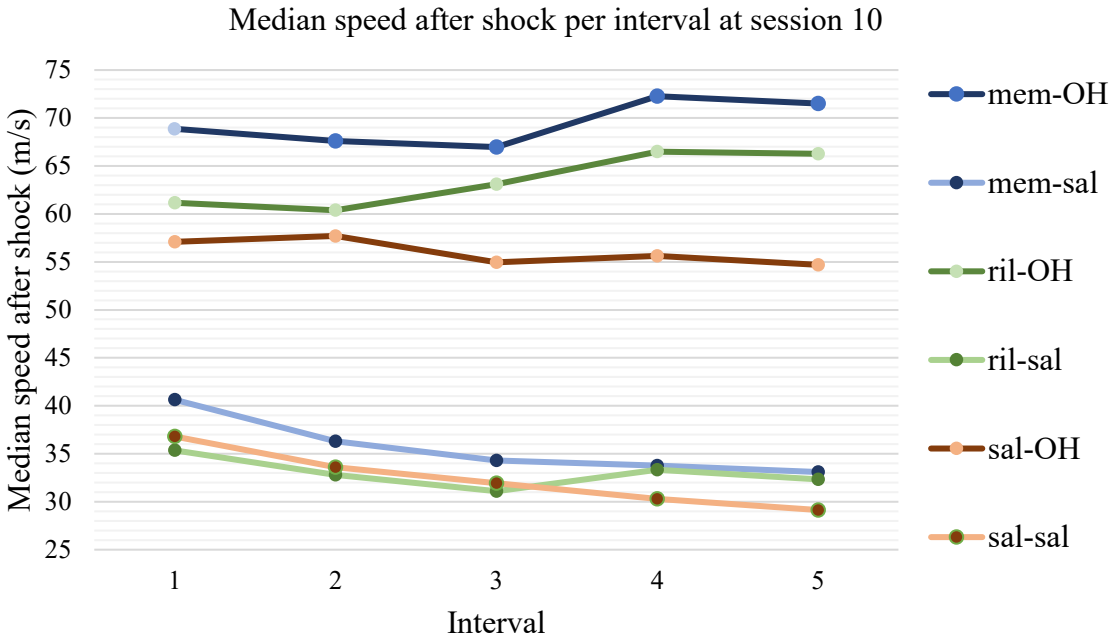
5.5 The median speed after shock during acquisition

Median speed after shock measures the startle reaction after the shock, and the ability to generate escape reaction, hence the ability to perceive the foot-shocks. It should be noted that this parameter did not reflect whether the escape was directed to a safe place or a different location within the sector. According to the Shapiro-Wilk test, data were normally distributed, and three-way RM ANOVA was performed. Assumption of sphericity was not met, therefore the Greenhouse-Geisser correction was used. Analysis showed main effect of interval [$F(1.848, 160.759) = 6.557$, $p < 0.002$], interval x treatment [$F(9.239, 1649.122) = 2.453$, $p < 0.01$] and session x treatment interaction [$F(13.920, 1211.081) = 3.750$, $p < 0.001$]. However, Games-Howell post hoc

test revealed 8-OH-DPAT (means of median speed after shock at session 10: Mem-OH = 69 m/s, Ril-OH = 63 m/s, Sal-OH = 58 m/s) groups differed from the saline groups (means of median speed after shock at session 10: Mem-Sal = 36 m/s, Ril-Sal = 33 m/s, Sal-Sal = 32 m/s) again, with memantine and riluzole even increasing the median speed after shock (graph 8, 9 and figure 13). In the saline groups, many animals did not receive any shocks during the last session. The 8-OH-DPAT groups were overall faster e, which suggests hyper-reactivity to shocks. The data, however, rule out the possibility that the learning deficit could have been caused by the impaired perception of the shocks.



Graph 8: The median speed after shock per session. *Saline groups were significantly slower in contrary to 8-OH-DPAT groups. The saline-8-OH-DPAT group had a slower escape than memantine-8-OH-DPAT and riluzole-8-OH-DPAT. However, this finding shows that all groups perceived the shock and tended not to stay in the sector. X-axis – Daily sessions, Y-axis – Median speed after shock (m/s).*



Graph 9: The median speed after shock per intervals in the final session. *As can be seen, saline groups were slower after the shock. 8-OH-DPAT treated groups were faster and groups Ril-OH and Mem-OH were getting faster throughout the session. X-axis – 10-min intervals, Y-axis – Median speed after shock (m/s).*

Means at session 10 (S.E.M)	**Sal-OH**	**Sal-Sal**	**Mem-OH**	**Mem-Sal**	**Ril-OH**	**Ril-Sal**
Total distance (m)	275 (±20)	162 (±3.9)	353 (±26.3)	178 (±5.7)	318 (±21.3)	165 (±4)
Entrances	69 (±20.4)	2 (±0.3)	77 (±25.5)	3 (±0.6)	99 (±20.5)	2 (±0.4)
Shocks	115 (±31)	4 (±1.8)	133 (±41.9)	5 (±2.8)	161 (±33.7)	2 (±0.4)
M. speed after shock (m/s)	58 (±4.3)	32 (±9.9)	69 (±7.6)	36 (±16.6)	63 (±3.6)	33 (±8.8)

Figure 13: Means of all parameters during the final session with standard errors of the means in the brackets

6 Discussion

This study tested the spatial learning abilities 8-OH-DPAT-induced rat model of OCD, to evaluate the validity of this model tested by other authors (Alkhatib et al., 2013; Yadin et al., 1991) and the effect of glutamatergic agents memantine and riluzole on cognitive deficits in OCD in this model. This hypothesis was based on the indications of elevated levels of glutamate in OCD patients (Ting & Feng, 2008) and preliminary successful results of off-label case studies with these drugs (Grant et al., 2014; Pittenger et al., 2015). Cognitive deficits were reported in OCD patients and they were reported to have problems with memory and learning (reviewed in (Gruner & Pittenger, 2017). Specifically, this experiment tested spatial learning impairments in an active place avoidance task requiring spatial learning and cognitive coordination in an 8-OH-DPAT- induced model and it focused on sensitized and acutely treated animals as well as sensitized, but untreated animals. The effects of riluzole and memantine on possible deficits induced by sensitization and treatment with 8-OH-DPAT were revealed to contribute to the elucidation of roles of these drugs in OCD therapy.

6.1 Hyperlocomotion induced by 8-OH-DPAT sensitization

First, we tested the 8-OH-DPAT-induced model in the rotating arena without shocks. Rats were habituated to the arena and sensitized to the drug by 10 injections. Systemic administration of 8-OH-DPAT (0.25mg/kg) immediately before the 50-min session in the arena elicited a strong hyperlocomotion in 8-OH-DPAT rats compared to controls. It appears that in this sense 8-OH-DPAT sensitization represents a valid animal model of OCD. This finding can be related to previous studies, in which acute (not chronic) 8-OH-DPAT administration at a dose of 1 mg/kg created perseverative behavior in a T-maze, nevertheless, it also decreased locomotion behavior and the dose of 2 mg/kg abolished T-maze learning almost completely (Odland et al., 2019). Both doses are much higher than the dose we used in the present study (0.25 mg/kg) and

applied only acutely. Compulsive checking and hyperlocomotion in an open-field arena 60min after acute administration of 8-OH-DPAT (5 mg/kg) was observed by Evenden and Ängeby-Möller (1990). This followed a 30-min period of decreased locomotion. At a lower dose (1.5 mg/kg), the motor inhibition lasted for a shorter time and the hyperactive behavior began earlier after the injection and at the lowest dose (0.5 mg/kg), no inhibition of locomotion was seen and the injection immediately produced hyperlocomotion (Evenden & Ängeby-Möller, 1990). This agrees with decreased motor activity in rats after acute 8-OH-DPAT administration (2 mg/kg) in a study made by Hillegaart, Wadenberg, & Ahlenius (1989). The above-mentioned doses are much higher than the dose we used in the present study (0.25 mg/kg), hence there is a probable dose-dependent 8-OH-DPAT effect with the higher dose inhibiting locomotion. Chronic administration of 8-OH-DPAT at small doses (0.0625, 0.125 mg/kg) per 8 days does produce hyperlocomotion and compulsive checking even when tested after several days without the 8-OH-DPAT and after saline injections (Johnson & Szechtman, 2016). This suggests, that lower doses of 8-OH-DPAT that are chronically administered create better models of OCD, because of their effects on locomotion and induction of compulsive behavior than acute higher doses of 8-OH-DPAT, which inhibit motor behavior and locomotion in a rat. Nevertheless, at our doses of 0.25 mg/kg 8-OH-DPAT, every other day for 10 sessions during the habituation phase did not affect the animals later in the acquisition phase, if they were not also acutely treated during acquisition.

6.2 A deficit in spatial learning induced by 8-OH-DPAT sensitization

Second, we tested the effects 8-OH-DPAT sensitization and acute treatment vs. only sensitization on spatial learning in an active place avoidance task on Carousel in the spatial version (with the to-be-avoided sector defined in room frame). Administration of 8-OH-DPAT (0.25mg/kg) to previously sensitized rats before 50-minutes in a rotating arena in acquisition showed learning impairments and again,

strong hyperlocomotion. The animals that received 8-OH-DPAT were more active and had greater number of errors (entrances to the shock sector) contrarily to the saline controls. However, the chronic sensitization to 8-OH-DPAT in habituation without acute application during acquisition did not affect spatial performance or locomotion. Only the groups that were injected with 8-OH-DPAT also in acquisition showed impaired spatial learning. Animals on 8-OH-DPAT were also faster in escape after receiving a shock than the control group, nevertheless, they did not always escape to the safe place, hence they received an overall greater number of shocks in the acquisition. This suggests that they had preserved nociception and the drug did not alter their perception of the shocks. However, they could not learn the position of the "to-be-avoided" sector. This is in agreement with previous findings of perseverative behavior (Odland et al., 2019), deficits in decision-making processes (Yadin et al., 1991) and compulsive checking (Alkhatib et al., 2013) observed in 8-OH-DPAT induced models. Despite it was shown that 8-OH-DPAT has analgesic effects in a formalin model of tonic nociception in a rat (Bardin, Tarayre, Koek, & Colpaert, 2001) our data suggest unaltered perception of the shocks in our model. These effects of 8-OH-DPAT may have been caused by inhibition of the serotonin-negative feedback loop, normally lowering the drive of the dopaminergic system (Alkhatib et al., 2013). The sensitization and subsequent acute treatment with 8-OH-DPAT may keep the dopaminergic system highly activated and thus create hyperlocomotion and compulsive and perseverative behavior.

6.3 No effect of memantine and riluzole on the 8-OH-DPAT model

6.3.1 Chronically sensitized but untreated animals

There were no cognitive impairments in chronically-only sensitized animals in the acquisition and there was no effect of memantine or riluzole. This contrasts with the results of the only chronic administration effects made by Szechtman (2016). Their results revealed an effect of chronic administration with smaller doses (0.0625, 0.125

mg/kg) on locomotion and cognitive functions even after several days without the 8-OH-DPAT injections. It is difficult to explain this contradiction with the present data; nonetheless, it appears that there is no effect of memantine and riluzole (1 mg/kg) on cognitive functions without the acute 8-OH-DPAT application.

6.3.2 Chronically sensitized and acutely treated rats,

The main finding of this study was that neither riluzole nor memantine alleviated the deficits in learning or hyperlocomotion in an animal model of OCD created by chronic and acute administration of 8-OH-DPAT. Instead, both riluzole and memantine (1 mg/kg) aggravated these deficits.

The rats were even more hyperactive when they received riluzole or memantine before the 8-OH-DPAT than animals that received saline before the 8-OH-DPAT. This effect for the case of memantine could have been induced by the stimulatory effect of memantine itself. Higher doses (5 mg/kg) were found to produce hyperlocomotion (Réus et al., 2008) and dose-dependent (from 3 mg/kg) decrease of impulsivity, resulting in a perseverative behavior (Sukhanov, Zakharova, Danysz & Bespalov, 2004). At our doses (1 mg/kg) there was no effect of memantine itself without the acute 8-OH-DPAT administration. Regarding riluzole, a previous study showed decreased behavioral and motor activity as well as an analgesic effect; however, at a dose four-times higher (4 mg/kg) than we used in the present study (Kretschmer, Kratzer, & Schmidt, 1998). Riluzole at a dose of 1 mg/kg, which we used in our study, exerted no observable action in animals that did not receive 8-OH-DPAT during acquisition.

The numbers of entrances into the shock sector were significantly increased in the 8-OH-DPAT groups and the 8-OH-DPAT-riluzole/memantine groups had the most errors. They had only a very slight improvement over the whole acquisition testing and no improvement within a session. This shows markedly impaired spatial learning. This

is in agreement with no beneficial effect of memantine and riluzole on the quinpirole model of OCD (Janikova et al., 2019), but contrasts the positive memantine's effect in relieving serotonin-induced compulsive scratching behavior in mice (however, in this case at a ten-times higher dose (10 mg/kg) and added to fluoxetine) (Wald, Dodman, & Shuster, 2009). In a marble-burying model of compulsive behavior, memantine (10 mg/kg) was effective in suppressing the marble-burying behavior in rats without affecting locomotion. Riluzole (10 mg/kg) was not effective in alleviating marble-burying behavior at all, although it decreased motor behavior (Egashira et al., 2008).

The total number of shocks received was higher in those group, nevertheless, they were faster in escaping the shock sector than the saline groups, probably due to their overall hyperactivity, suggesting overt behavioral sensitization. This implicates that the animals could escape the unpleasant stimuli, however, their spatial learning was impaired. They also sometimes did not escape into the safe place after the shock. Therefore, they could feel the shocks and their deficits in the acquisition were not caused by freezing. One of the possible explanations for the results of our study is the interaction of memantine/riluzole with the 8-OH-DPAT and their action upon different structures. 8-OH-DPAT is presynaptically blocking AMPA receptors and glutamate release by 5-HT_{1A} receptors. Nevertheless, it also enhances AMPA activity postsynaptically and CA3-CA1 synaptic transmission in the hippocampus by being a 5-HT_7 receptor agonist. Additionally, 8-OH-DPAT modulated glutamate transmission induced by exogenous AMPA administration (Costa, Trovato, Musumeci, Catania, & Ciranna, 2012). Together with 8-OH-DPAT inhibiting LTP by 5-HT_{1A}, hence disturbing learning and memory, it could create the effect of learning impairment seen in this experiment, because both memantine and riluzole does decrease the glutamate levels even more. Besides the hippocampus, 8-OH-DPAT reduces excitation in the entorhinal cortex (Schmitz et al., 1998). 5-HT_{1A} and 5-HT_7 receptor inhibit glutamate transmission in the frontal cortex (cerebellum and many other structures involved in the motor and affective behavior) (for review see Ciranna, 2006).

Our results contradict the positive outcomes of antiglutamatergic treatment in OCD patients. Riluzole was shown as effective in several cases (Grant et al., 2010), however, it is not working for all of the patients, and studies done with riluzole are limited by their small sizes. Memantine was effective in several case studies (Pasquini & Biondi, 2006b; Poyurovsky et al., 2005) as well as in one randomized study (Kishi et al., 2018a). However, both memantine and riluzole were effective when given together with existing treatment with SSRIs (Aboujaoude et al., 2009; Kishi et al., 2018; Pittenger et al., 2008).

Our results are analogous as to those of the previous study from our laboratory, which showed that riluzole and memantine exerted similar exacerbating effects in an animal model of OCD induced by dopamine receptor agonists quinpirole (Janikova et al., 2019). Together this suggests that these models are not responsive to antiglutamatergic monotherapy by riluzole or memantine in smaller doses. Taken together, higher doses of memantine or riluzole are needed to affect symptoms of animal models of OCD. However, such doses are often accompanied by side-effects, such as motor inhibition or analgesia. Our results suggest that the interconnection of neurotransmitter systems is more intense and important and hence antiglutamatergic drugs may interfere with serotonin/dopamine drugs used to create animal models of OCD. Also, our results support the concept that glutamate modulating or antiglutamatergic agents such as riluzole or memantine are not alleviating OCD symptoms at small doses and in monotherapy.

7 Conclusion

The present study reproduced cognitive deficits created by the 8-OH-DPAT model. It showed hyperlocomotion and learning and memory impairments in the Carousel maze. However, chronic administration of 8-OH-DPAT only during the habituation did not affect learning in the acquisition phase. Acute administration of 8-OH-DPAT elicited hyperlocomotion and spatial learning deficit. Drugs that are antagonizing (memantine) or modulating the glutamatergic system (riluzole), had no alleviating effect on place learning deficit in an active place avoidance task induced by 8-OH-DPAT sensitization and treatment, perhaps since the antiglutamatergic agents may interfere with the 8-OH-DPAT and reduce glutamate levels in specific brain areas to a point where learning was strongly compromised.

8 Bibliography

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