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Mgr. et Mgr. Martina Janíková

Cognitive flexibility in selected animal models of psychiatric disorders
Kognitivní flexibilita ve vybraných animálních modelech psychiatrických onemocnění

Ph.D. Thesis

Supervisor: prof. RNDr. Aleš Stuchlík, DSc.

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Identifikační záznam

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Abstrakt

Kognitivní flexibilita představuje schopnost adaptivně měnit své chování či způsob přemýšlení v závislosti na vnějších podmínkách. Kognitivní rigidita byla popsána u řady psychiatrických a neurovývojových onemocnění, včetně její role v rozvoji a udržování některých symptomů. V této práci jsme se proto zaměřili na studium kognitivní flexibility a dalších behaviorálních charakteristik v několika animálních modelech relevantních ke schizofrenii, obsedantně-kompulzivní poruše a poruše autistického spektra. V myším "two-hit" modelu schizofrenie jsme našli rozdíl mezi skupinami v *set-shiftingu* a snížený počet parvalbuminových interneuronů v hipokampu u stresovaných myších samic. Překvapivě jsme nezjistili zhoršení v žádném jiném behaviorálním testu. Ve dvou farmakologických potkaních modelech relevantních k OCD jsme ukázali, že agonista dopaminových D2/D3 receptorů quinpirole a agonista serotoninových A1/7 receptorů 8-OH-DPAT způsobily natolik závažné poruchy prostorového učení a paměti v úloze aktivního vyhýbání se místu, že nebylo možné testovat reversal. Léky snižující glutamátergní neurotransmisi, memantin a riluzol, překvapivě ještě prohloubily tento deficit, přestože žádný takový efekt nebyl pozorován v případě, kdy byly aplikovány samostatně. Dále jsme ukázali, že *knockout* CRMP2 (collapsin response mediator proteinu 2) způsobuje behaviorální i neurobiologické změny relevantní k poruchám autistického spektra. Myši s delecí CRMP2 měly defekty v navádění axonů a prořezávání a remodelaci dendritických trnů. Objevila se u nich snížená sociální interakce v postnatálním období i v dospělosti, zvýšená perseverace ve Y-maze a snížená úzkost ve vyvýšeném křížovém bludišti. Překvapivě měli normální výkon v úloze aktivního vyhýbání se místu, což naznačuje zachovanou prostorovou paměť a kognitivní flexibilitu.

Klíčová slova: Kognitivní flexibilita, animální modely, schizofrenie, obsedantně kompulzivní porucha, porucha autistického spektra

Abstract

Cognitive flexibility is the ability to adjust thinking and behavior based on changing conditions. Cognitive rigidity has been described in a variety of psychiatric and neurodevelopmental disorders and has been suggested to contribute to symptom maintenance. Therefore, we aimed to study cognitive flexibility and other behavioral characteristics in several rodent models relevant to schizophrenia, obsessive-compulsive disorder, and autism spectrum disorder. In a two-hit mice model relevant to schizophrenia, we found the between-group difference in set-shifting and decreased number of parvalbumin interneurons in the hippocampus of stressed female mice. Interestingly, we found no impairment in any other behavioral task. In two pharmacological rat models relevant to OCD, we showed that sensitization to D2/D3 receptor agonist quinpirole and serotonin 1A/7 agonist 8-OH-DPAT produced severe spatial learning and memory impairment in the Active Allothetic Place Avoidance task. The impairment was so severe that the reversal couldn't be tested. Surprisingly, drugs decreasing glutamatergic neurotransmission, memantine and riluzole, further impaired the performance in both models, although no such effect was observed when they were applied alone. Lastly, we showed that the knockout of a collapsin response mediator protein 2 (CRMP2) produced behavioral and neurobiological impairments relevant to autism spectrum disorder. CRMP2 knockout mice had defects in axonal guidance, pruning, and dendritic spine remodeling, decreased social interaction in the postnatal period and adulthood, increased perseveration in the Y-maze and decreased anxiety in the Elevated Plus Maze. Surprisingly, they had normal spatial memory and reversal learning in the Active Allothetic Place Avoidance task.

Keywords: Cognitive flexibility, animal models, schizophrenia, obsessive-compulsive disorder, autism spectrum disorder

List of Abbreviations

8-OH-DPAT	8-hydroxy-2-(di-n-propylamino) tetralin
AAPA	Active Allothetic Place Avoidance task
ACC	Anterior cingulate cortex
ACC	Anterior cingulate cortex
AMPA	α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid
APO-SUS	Apomorphin susceptible
ASD	Autism spectrum disorder
CA1/2/3	Cornus amoni
CANTAB	Cambridge Neuropsychological Test Automated Battery
CNO	Clozapine-N-oxide
CNS	Central nervous system
COMT	Catechol-O-methyltransferase
COMT-Val/Met	Catechol-O-methyltransferase gene polymorphism for valine/ methionine
CRMP2	Collapsin response mediator protein 2
CSTC	Cortico-striato-thalamo-cortical circuits
dAI	Dorsal anterior insula
DAT	Dopamine transporter
DISC1	Disrupted in schizophrenia 1
DMN	Default mode network
DREADD	Designer Receptors Exclusively Activated by Designer Drugs
dPFC	Dorzolateral prefrontal cortex
ED	Extradimensional
EPM	Elevated Plus Maze
fMRI	Functional magnetic resonance imaging
GABA	Gamma-aminobutyric acid
GAD	Glutamic acid decarboxylase
GD	Gestational day
ID	Intradimensional
IFJ	Inferior frontal junction
IED	Intra-Extra Dimensional Set Shift task (CANTAB battery)

IQ	Intelligence quotient
KO	Knockout
LSD	Lysergic acid diethylamide
LTD	Long-term depression
LTP	Long-term potentiation
MAM	Methylazoxymethanol acetate
MIA	Maternal immune activation
MK-801	Dizocilpin
mPFC	Medial prefrontal cortex
mRNA	Messenger Ribonucleic acid
MWM	Morris Water Maze
NAc	Nucleus accumbens
NMDARs	N-methyl-D-aspartate receptors
NVHL	The neonatal ventral hippocampal lesion
OAT	Object alteration task
OCD	Obsessive compulsive disorder
OFC	Orbitofrontal cortex
PCP	Phencyclidine
PD	Prenatal day
PFC	Prefrontal cortex
Poly(I:C)	Polyinosinic:polycytidylic acid
PPI	Prepulse inhibition of the startle reflex
PPC	Posterior parietal cortex
PVIs	Parvalbumin-expressing interneurons
SSRIs	Selective serotonin reuptake inhibitors
STN	Subthalamic nucleus
TMT	Trail Making Test
USV	Ultrasonic vocalization
VAChT	Vesicular acetylcholine transporter
VGLUT	Vesicular glutamate transporter
VMS	Ventromedial striatum
WCST	Wisconsin Card Sorting Test
WT	Wild-type

Preface

Cognitive flexibility plays an important role in our everyday lives. It helps us when we need to switch from one activity to another, modify our behavior according to situational changes or understand the point of view of others. Its disruption has been described in several psychiatric or neurodevelopmental disorders. Furthermore, cognitive rigidity has been suggested as one of the hallmark features of obsessive-compulsive disorder (OCD) or autism spectrum disorder (ASD) (Gruner & Pittenger, 2017; Scarpa et al., 2021). Notably, decreased cognitive flexibility has also been described in healthy relatives of patients with OCD, showing that cognitive rigidity might be part of the OCD endophenotype (Chamberlain et al., 2007). Furthermore, some authors suggest that cognitive rigidity is an important factor in the development and maintenance of psychiatric symptoms, as the patients are stuck in inflexible thought and behavior patterns (Moritz & Woodward, 2007).

This thesis is focused on cognitive flexibility in executive functions, mainly on spatial learning and cognitive flexibility in rodent models relevant to schizophrenia, OCD, and ASD. Furthermore, other related behavioral and neurobiological findings are described. The thesis is based on four original articles published in journals with an impact factor.

In the first paper, **Selective deficits in attentional set-shifting in mice induced by maternal immune activation with poly(I:C),** we assessed behavioral characteristics and changes in hippocampal parvalbumin interneurons in a two-hit mice model relevant to schizophrenia. My colleague Kristýna Malenínská and I were responsible for the model induction, conducted all behavioral experiments, verification of cytokines with ELISA, immunohistochemical staining (with the help of Dominika Radostová), and all data analysis. We also wrote the text of the manuscript.

In the second paper **No effect of riluzole and memantine on learning deficit following quinpirole sensitization – An animal model of obsessive-compulsive disorder,** we assessed cognitive impairment in rat model relevant to OCD based on quinpirole sensitization. Furthermore, we examined the effect of memantine and riluzole on alleviating the deficit caused by quinpirole sensitization. I participated in conducting the behavioral experiments and, together with Hana Brožka, analyzed all data and prepared the text and figures for the manuscript.

In the third paper, **Memantine and Riluzole Exacerbate, Rather Than Ameliorate Behavioral Deficits Induced by 8-OH-DPAT Sensitization in a Spatial Task**, we examined cognitive functions in another rat model relevant to OCD, which is based on 8-OH-DPAT sensitization. Again, we assessed the effect of memantine and riluzole, drugs decreasing glutamatergic neurotransmission. I participated in behavioral experiments, analyzed all data, and, together with Karolína Mainerová, prepared the text and figures for the manuscript.

In the fourth paper, **CRMP2 mediates Sema3F-dependent axon pruning and dendritic spine remodeling**, we studied the role of a collapsin response mediator protein 2 (CRMP2) in neurodevelopment and autism spectrum disorder. CRMP2 full knockout mice were developed in the Laboratory of Molecular Neurobiology for that purpose. I conducted all behavioral experiments and, in collaboration with Jakub Žiak, the behavioral data analysis.

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1 Introduction

1.1 Types of cognitive flexibility

Cognitive flexibility is often defined as *„the ability to appropriately adjust one's behavior according to a changing environment"* (Dajani & Uddin, 2015, p. 571). It is a complex, higher-order cognitive skill mainly related to executive functions. As such, it is influenced by several cognitive functions, like planning, organizing, working memory, attention and inhibition (Dajani & Uddin, 2015). This multimodal nature makes the concept of cognitive flexibility ambiguous. Furthermore, several similar concepts are used in the literature, such as psychological, mental, or behavioral flexibility.

Psychological flexibility is a concept widely used within Acceptance and Commitment Therapy. It can be understood as an ability to successfully navigate in changing conditions, even when faced with difficult situations, and manage thoughts and responses (Hoffmann et al., 2019). Psychological flexibility is thought to be related to coping strategies and psychological well-being (Tindle et al., 2021). Cognitive and psychological flexibility are close, partially overlapping concepts. However, psychological flexibility is more often used in a psychotherapeutic context, while cognitive flexibility in cognitive psychology and neuroscience research. Psychological flexibility also differs from cognitive flexibility in the emphasis on being mindfully present at the moment, long-term personal values, self and committed action (Ramaci et al., 2019). Therefore, psychological flexibility is outside the scope of this thesis and will not be further elaborated.

1.1.1 Flexibility in executive functions

Cognitive flexibility is most often described and measured in terms of executive functions. Executive functions include a wide array of psychological functions, mainly attention, planning, task initiation, ongoing process monitoring, task completion and inhibition (Friedenberg & Silverman, 2006). In this sense, cognitive flexibility refers to the ability to switch between multiple cues, goals, tasks, or activities based on their changing importance. However, cognitive flexibility is a broader concept that also incorporates flexibility in reasoning, including generating several solutions to life situations, seeing different explanations of events, or changing opinions based on new information.

Reversal learning

Reversal learning focuses on the ability to adapt to changing reward contingencies of different stimuli. Experimental subjects first must learn to discriminate between two cues (discrimination learning). One of those cues becomes relevant by indicating a hidden reward or correct answer. After a successful acquisition, the relevance of the cues switches, and the formerly relevant cue becomes irrelevant and vice versa (Izquierdo & Jentsch, 2012). Several parameters can be measured in experimental set-ups using reversal learning, mainly the number of trials to reach the learning criterion or perseveration (preference for formerly relevant cue). Reversal learning often doesn't include strategy switching because the significant dimension or rule remains the same, so it represents a simpler version of flexibility assessment.

Attentional set-shifting

Attentional set-shifting refers to transitions between different mental „sets", which can be understood as relevant aspects of stimuli, e.g., smell and texture, color and pattern (Ravizza & Carter, 2008). In attentional set-shifting, the first stage is an acquisition of a rule, followed by a reversal stage, in which the relevance of cues switches (for example, the reward is now found in the arm unrewarded in the acquisition phase and vice versa). The next stage is usually an intra-dimensional shift, in which new cues are presented, followed by a reversal and then an extra-dimensional shift, in which an entirely new dimension or rule is introduced and becomes the relevant one, while the previously relevant cue turns into irrelevant (for example reward can be found according to scent and not texture, or cards should be sorted according to shape and not color). Therefore, strategy switching might be necessary for a successful task solution (Tait et al., 2018).

1.1.2 Flexibility in reasoning

Mental flexibility and perspective taking

Besides executive flexibility, cognitive flexibility is also understood as *„the ability to perceive multiple alternative explanations for life occurrences and human behavior"* and *"the ability to generate multiple alternative solutions to difficult situations"* (Dennis & Vander Wal, 2010, p. 243). This approach to cognitive flexibility emphasizes 1) empathy and social skills, such as looking at the situation from the point of view of another person or assessing multiple aspects of the situation before jumping to a conclusion and 2) problem-

solving and a tendency to think adaptively, rather than maladaptively. In this sense, cognitive flexibility also involves an aspect of creativity (e.g., trying to generate several solutions to a problem).

Explanatory flexibility

Explanatory flexibility is related to attributional styles and plays a role in explaining events in our life, especially whether we consider specific situational factors (Zhu et al., 2021). Higher explanatory flexibility has been associated with better adjustment to adverse life events (Fresco et al., 2007).

Belief flexibility

Belief flexibility is the „*metacognitive capacity of reflecting on one's own beliefs, changing them in light of reflection and evidence and generating and considering alternatives*" (Zhu et al., 2021, p. 2). Simply said, it is a willingness to change one's beliefs when encountering new evidence and acknowledging the possibility of being mistaken. Lower belief flexibility has been linked to higher delusional thinking, persecutory ideation and schizotypy even in the clinically healthy population (Bronstein et al., 2017; Bronstein et al., 2019).

1.2 Methods of measuring cognitive flexibility

1.2.1 Assessment of cognitive flexibility in humans

Reversal learning and set-shifting

Cognitive flexibility in humans is standardly measured by cognitive tests that focus on the participant's ability to adjust their responses based on changes in reinforcement. The gold standard is the Wisconsin Card Sorting Test (WCST), which has manual and computerized versions. The WCST consists of four stimulus cards and two card packs with 64 response cards. Cards differ in geometric shapes presented on them, number, and color of the shapes. Participants are asked to sort the response cards to one of the stimulus cards. The rule is not explicitly explained, so they have to find it out themselves according to the feedback (right x wrong). During the task, the rule switches several times, always after ten consecutive correct answers and without the participant being informed of the change. The test continues until six categories are completed or until the participant uses up all the cards. Several parameters are measured in the test, mainly the number of categories completed, which refers to ten consecutive correct answers, trials to complete the first category (number of cards necessary to complete the first category), the total number of errors and the number of perseveration errors, which reflects the failure to abandon previously correct sorting rule after it has been changed (Heaton et al., 1993). Perseverative errors are thought to reflect a deficit in behavioral inhibition (Landry & Mitchell, 2021). Apart from inhibition, reversal tasks measure reward learning and learning from feedback and reversal tasks with more than two options also explorative and exploitative strategies (Izquierdo et al., 2017).

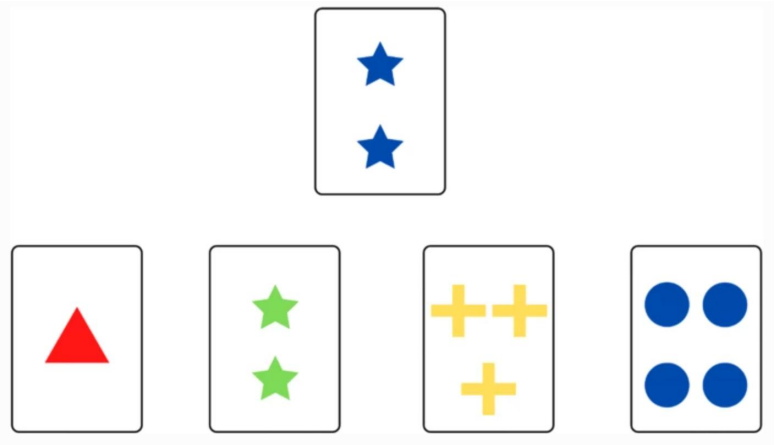

Figure 1: An example of the WCST task. Four stimulus cards and a sequence of response cards are presented to a participant, and he is asked to sort the response cards according to feedback (Retrieved from Miles et al., 2021).

Several computerized tests have been developed based on the WCST, like the CANTAB Intra-Extra Dimensional Set Shift Task (IED) or the Berg's Card Sorting Test in PEBL software. All these tests are sensitive to changes in the frontostriatal area, as impaired performance in set-shifting tasks has been described in patients with frontal lobe lesions (Owen et al., 1991; Tsuchida & Fellows, 2013; Yochim et al., 2007) and also frontal lobe epilepsy (McDonald et al., 2005).

Probabilistic reversal learning

Probabilistic reversal learning tasks are similar to non-probabilistic reversal tasks, but they include the component of uncertainty. Participants are presented with two or more stimuli and should find and stick to the one that more likely leads to a reward (usually in 80% of cases). After a successful acquisition, the reward contingencies are changed without prior notice (Izquierdo et al., 2017; Jara-Rizzo et al., 2020). Because the right choice is not always rewarded, this task enables researchers to evaluate the influence of positive and negative feedback on behavior.

Spatial cognitive flexibility

Spatial cognitive flexibility tasks have high translational potential, as many animal tests of cognitive flexibility are spatial-based (see Chapter 2.2.2). Several human spatial cognitive flexibility tasks have been inspired by animal set-shifting or working memory tasks that involve spatial navigation and changes in reward or goal location as a central task procedure.

One such task is the Blue Velvet Arena, an analog of the Morris Water Maze (MWM) for human subjects. It is a 2.8-meter-wide tent with spatial cues marked on the walls and starts and goal positions marked on the floor. The goal mark is then switched off, and the participants have to remember the position and navigate there from different start positions (Hort et al., 2007). The Blue Velvet Arena also has a computer version with several modifications. One of them is the Four Goals Navigation task, which is again inspired by protocols from the MWM (Fajnerová et al., 2014). Also, many other virtual maze tests on spatial navigation and cognitive flexibility have been developed, such as the Virtual Cognitive Flexibility Labyrinth based on the WCST (Delahaye et al., 2015) or the maze based on the MWM in immersive virtual reality (Commins et al., 2020).

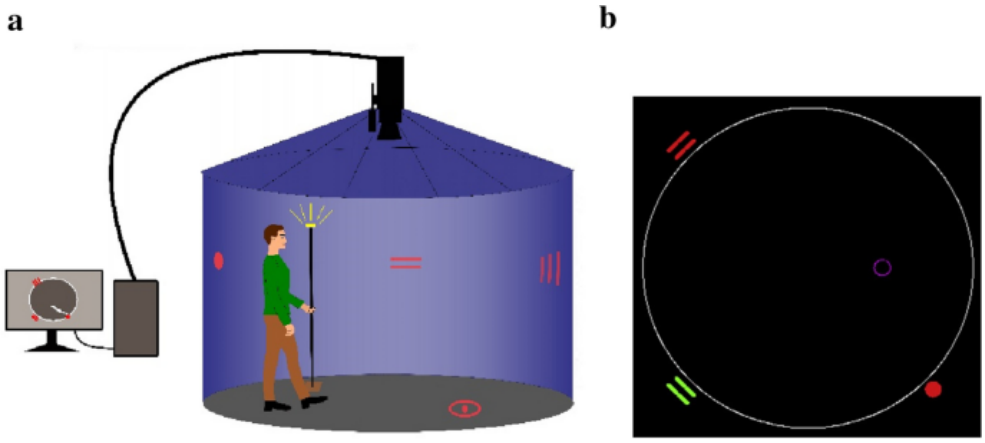

Figure 2: A) The Blue Velvet Arena is a real-space human analog of the Morris Water Maze, based on egocentric or allocentric navigation to a hidden goal. B) Schematic illustration of an aerial view of the arena shows an example of an experimental set-up (Retrieved from Němá et al., 2021).

Other tasks related to cognitive flexibility

Cognitive flexibility in humans can be further tested by several standardized tests that are also related to processing speed and attention, such as the Trail Making Test B or the Stroop Color and Word Test, and also by tests of creativity, as cognitive flexibility involves an ability to generate new responses or ideas to solve a particular situation. Flexibility in reasoning may be assessed by tasks and inventories, such as Bias Against Disconfirmatory Evidence (Woodward et al., 2006) or the Cognitive Flexibility Inventory (Dennis & Vander Wal, 2010).

1.2.2 Assessment of cognitive flexibility in mice and rats

Attentional set-shifting

The paradigm for attentional set-shifting in rodents has been developed according to tests for humans and monkeys. Firstly it was designed for rats (Birrell & Brown, 2000) and later adjusted for mice (Colacicco et al., 2002). The test consists of a plastic cage divided into three chambers by sliding doors. One part is used as a waiting chamber, and two as choice chambers. The rat or mouse is trained to dig and find a food reward hidden in one of two bowls presented in the stimulus chambers (one in each compartment). The bowls are filled with different digging mediums and may also differ in odor and texture, covering the surface.

In the habituation phase, the rodents are food restricted to reduce their body weight to approximately 85% of the free-feeding weight. They are also habituated to bowls with digging mediums and hidden food rewards. In the training phase, they are given free access

to all the chambers in the first four trials, so they can explore the arena and dig in both bowls to find a food reward. From trial five, they are allowed to dig in one bowl only, and their choices are recorded. The testing continues until the rodent reaches the criterion of six consecutive correct choices. Afterward, the second dimension is introduced without changing the relevant dimension. All relevant dimensions remain the same for the reversal phase, but the previously correct stimulus becomes incorrect and vice versa. In the intra-dimensional (ID) shift, the relevant dimension remains the same as before, while in the extra-dimensional (ED) shift, the previously irrelevant dimension becomes relevant (from digging medium to odor or vice versa). There are several types of odors, digging media and textures covering the bowl so that researchers can combine them according to their specific experimental design (Birrell & Brown, 2000; Colacicco et al., 2002).

Another version is an operant lever-pressing task (as described, for example, in Brady & Floresco, 2015) or a touchscreen-based set-shifting task that is even more similar to attentional set-shifting tasks used with humans or monkeys. Touchscreen task requires presenting two types of visual stimuli with two perceptual dimensions (e.g., shapes and lines) on a touchscreen and training the mice or rats to indicate a choice by a nose-poke (Brigman et al., 2005; Dickson et al., 2014). Also, a newer version of the touchscreen task has been developed, which presents two reinforced stimuli and a third never-reinforced stimulus (Piantadosi et al., 2019). An advantage of touchscreen tasks lies in high external and internal validity. On the other hand, it requires special device and long training of mice/rats, which may take up to several months (Garner et al., 2006).

In general, the rodent subjects should perform worse in ED shifts than in ID shifts (Birrell & Brown, 2000; Garner et al., 2006; Young et al., 2010), suggesting they successfully formed an attentional set (Birrell & Brown, 2000). Although in mice, the difference between ID and ED shifts was not always described (Brigman et al., 2005; Colacicco et al., 2002).

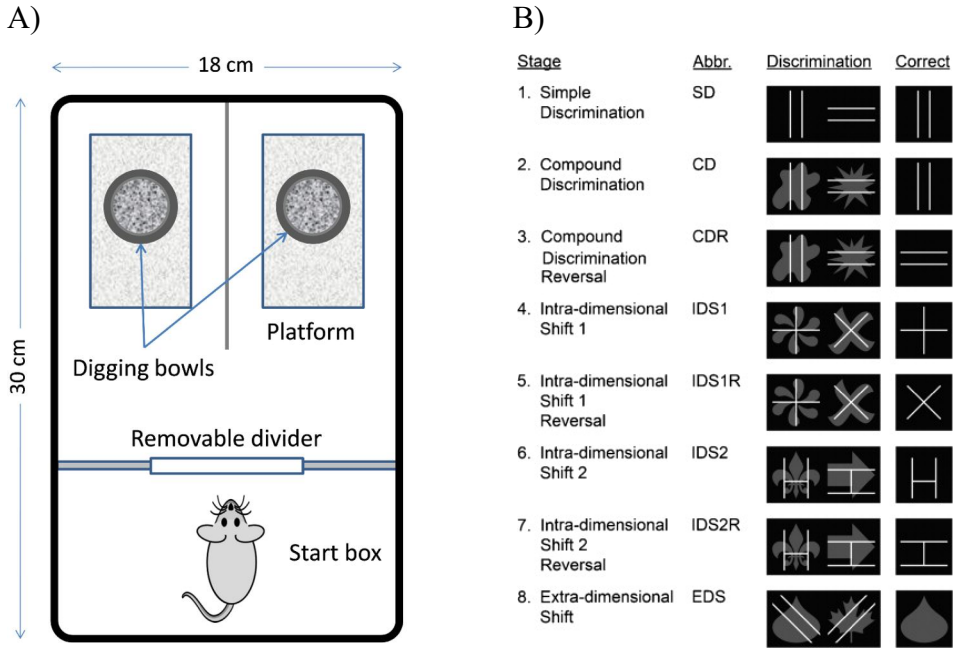

Figure 3: A) Schematic illustration of a classical digging set-shifting task for mice. B) An example of a visual touchscreen set-shifting task for rodents (Retrieved from Tanaka et al., 2011; Dickson et al., 2014).

Morris Water Maze

The Morris Water Maze has been developed for studying spatial memory in rats. A rat is trained to find an isle hidden under the water's surface. An isle is made from translucent material and, as such, is invisible to the rat. Therefore, the rat must learn to use spatial cues around the maze to successfully remember the isle's position. After a few days, the position of the isle is changed (Morris, 1984). Several protocols are used to measure different types of memory or other psychological domains. Cognitive flexibility can be measured in the reversal MWM task, in which the isle is relocated to a different, usually opposite, quadrant (Vorhees & Williams, 2006). The MWM takes advantage of rats being naturally good swimmers. However, the task may be significantly less suitable for mice because forced swimming may cause them a high amount of stress. Some mice also tend to float instead of actively swimming; in that case, the MWM cannot be credibly evaluated.

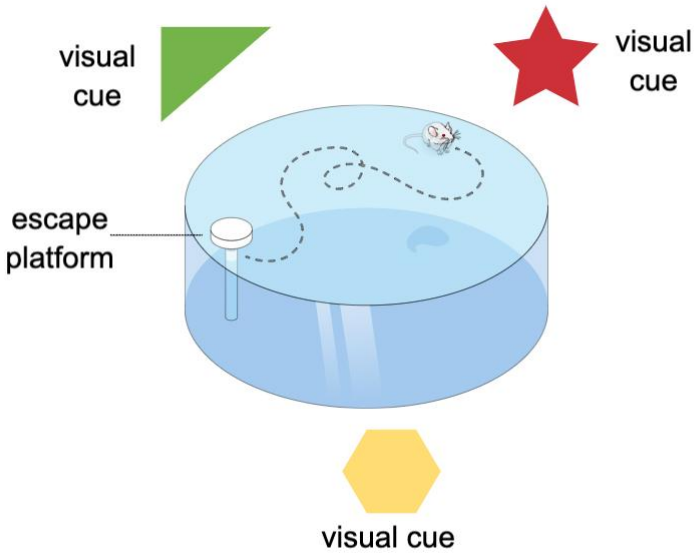

Figure 4: Schematic illustration of the Morris Water Maze. Rodents are trained to swim to the translucent escape platform hidden under the water's surface. Visual cues are distributed around the maze to facilitate orientation.

Barnes Maze

The Barnes Maze (Barnes, 1979) is a dry-land task based on rodents‘ aversion to open spaces, and as such, it may be a better alternative for mice experiments. It has been used to study spatial working memory, reference memory, and cognitive flexibility. The maze consists of a circular arena with 18 to 20 holes around its circumference (or slightly less for mice). An escape box is hidden under one of the holes, where the rodent may seek shelter, and visual cues are distributed around the maze to make the orientation easier. In the basic protocol of the Barnes Maze, the position of the escape box remains the same for several trials in the acquisition phase. Then it’s reversed (e.g., 135°) from the previous position in the reversal phase. The typical setup in the acquisition phase consists of two trials per day for five days for rats and four trials per day for four days for mice. The reversal phase is usually shorter and starts 24 hours after the last acquisition or probe trial (Gawel et al., 2019).

Active Allothetic Place Avoidance

The Active Allothetic Place Avoidance (AAPA) is a task developed by Jan Bureš at the Institute of Physiology CAS in Prague and has versions for both rats (Bures et al., 1997a; Bures et al., 1997b) and mice (Cimadevilla et al., 2001). The apparatus consists of a metallic disc surrounded by a transparent plexiglass. On the floor is a 60° invisible sector, where rodents receive a mild shock (0.2-0.6 mA) upon entering. Visual cues are again distributed

outside the arena (and inside for a set-shifting task). The arena rotates at a speed of one rotation per minute, so the rodents have to move to avoid the shock sector. Rodents may also be trained to forage for food rewards sequentially dropped in the maze (Bures et al., 1997b). In the acquisition phase, the rodents learn the position of the sector based on extra maze cues. In the reversal phase, the position of the shock sector is relocated to the opposite part of the arena. Apart from that, the sector may be stable relative to the room or relative to the arena and the frames might be switched to test other phases of set-shifting (Svoboda et al., 2015).

A) B)

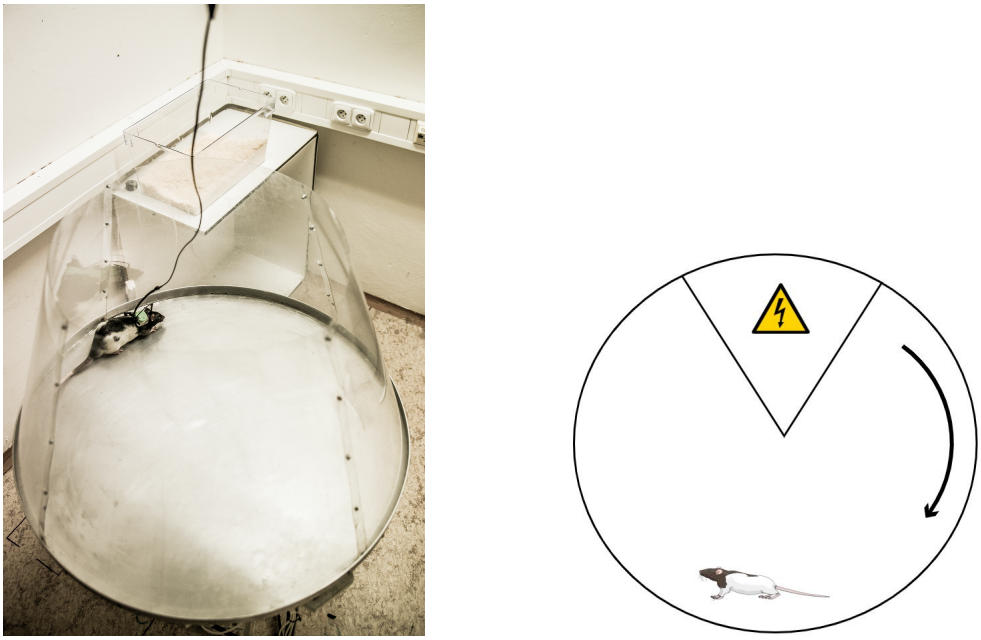

Figure 5: A) The Carousel maze (rotating arena) used for the AAPA (© Kristýna Malenínská). B) Schematic illustration of the experimental set-up.

Reversal and set-shifting in the T-maze or the cross maze

Simple spatial reversal learning can be tested in the T-maze, which is a T-shaped maze with one start arm and two goal arms (d'Isa et al., 2021). Rodents are trained to find a food reward in one of the goal arms. If they choose the right arm, they are allowed to eat the reward; if they choose the wrong one, they are blocked by sliding doors in the empty arm for a few seconds and then returned to the start position. The sliding doors can be controlled manually or automatically. After a successful acquisition, the reversal can be tested by changing an unrewarded arm into rewarded one and vice versa (Watson & Stanton, 2009).

Set-shifting can be further tested in the cross maze, like, for example, in the experimental set-up of Torres-Berrío et al. (2019). In the Cross maze, one of the arms is

blocked by a sliding door, thus creating a T-maze. The spatial set-shifting paradigm is based on switching navigation according to egocentric cues to navigation according to allocentric cues. During the habituation, rodents are allowed to freely explore the whole maze with food rewards placed in small food containers at the end of each arm. Twenty-four hours later starts the allocentric task. The visual cues are distributed around the maze, and the arms are identified according to cardinal points (North, South, East, West). The North arm is blocked, and the reward is always in the East arm, while the starting position alternates between the South and the West arms. Ten correct trials in a row within a session is considered a learning criterion. During the test phase, the start position is moved to the previously blocked North arm to see if rodents can find the reward from the new location. In the Egocentric task, the rodents start from either the South or the North arms and are trained to make a 90° turn left to find a food reward. During the test, the rodents start from the West arm to assess if they can find a food reward from the novel start position. The experiment takes 11 days: one habituation day and five days for each condition. Each session consists of 20 trials (Torres-Berrío et al., 2019).

Both the T-maze and the cross maze use positive reinforcement in the form of food reward, so the rodents should be food restricted and kept at approximately 85-95% of *ad-libitum* body weight since few days before the start of the experiment until the end of the experiment. They should be familiarized with the food reward before the first experimental day (Bicakci et al., 2021; Maleninska et al., 2022; Torres-Berrío et al., 2019). Both tasks represent simple and effective paradigms for studying cognitive flexibility without the necessity of purchasing special apparatus. Also, automatized versions are available nowadays, which prevents the experimenter effect. Inspired by the MWM, a water version of the T-maze or the cross maze exist, combining the benefits of both tasks (described, for example, in Phillips et al., 2013).

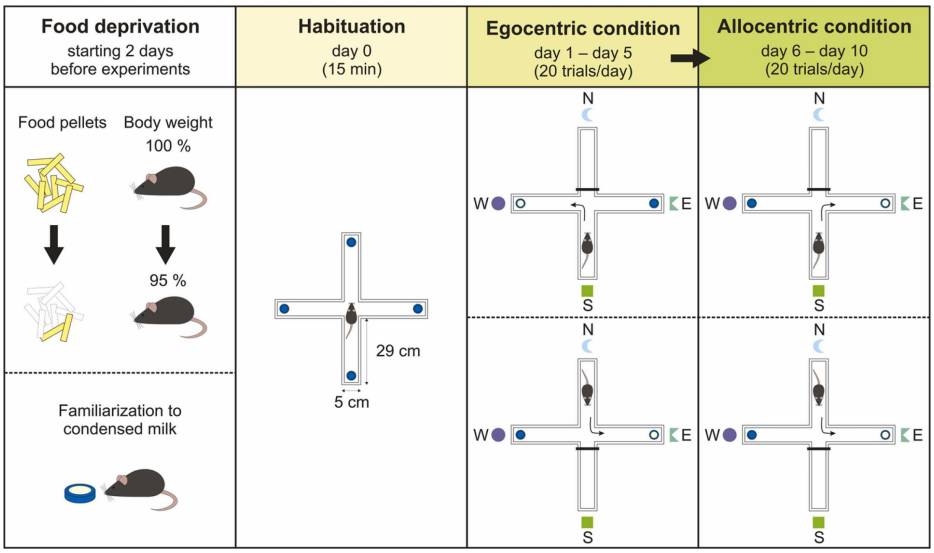

Figure 6: Illustration of a spatial set-shifting protocol in the cross maze. Mice are trained to find a food reward in one of the arms. In the egocentric condition, they always have to turn left; in the allocentric condition, the reward is always in the "East" arm (retrieved from Malenínská et al., 2022).

Spontaneous alternation in the Y-maze or the T-maze

Spontaneous alternation is not a hallmark test of cognitive flexibility; however, it measures willingness to explore new environments and uncovers rigid and perseverative behaviors. As such, it may be used and interpreted in relation to cognitive flexibility. Spontaneous alternation is a simple task that is based on a natural tendency to explore the environment and has been described not only in laboratory rodents and other mammals but also in non-mammals (d'Isa et al., 2021) and humans (Nguyen et al., 2017; Rothacher et al., 2020). It can be studied using the T-maze, or its alternative Y-maze, which has three equally sized arms marked as A, B and C. The experimental animal is placed into the A-arm and recorded for eight minutes. The experimenter writes down the sequence of visited arms and counts the percent of alternation (Prieur & Jadavji, 2019). Healthy animals should display an alternation of around 70-75% (d'Isa et al., 2021).

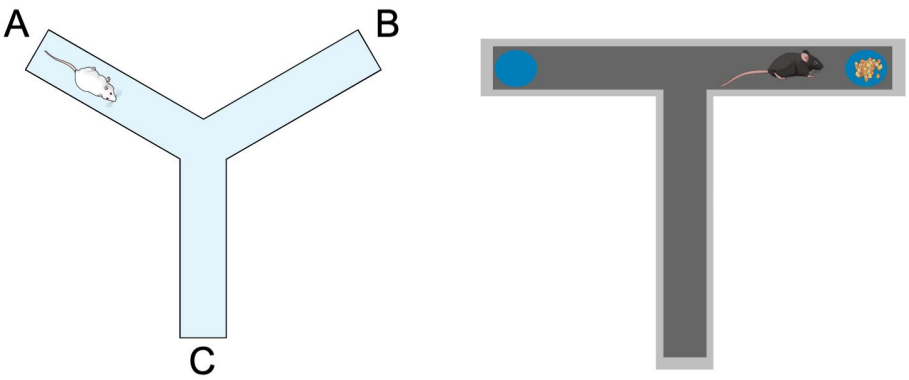

Figure 7: Schematic illustration of a spontaneous alteration in the Y-maze and rewarded alternation (or simple spatial reversal learning) in the T-maze.

1.3 Neural substrates of cognitive flexibility

As has been written earlier, several mental processes take part in cognitive flexibility, and so it is not easy to disentangle which brain areas underly which processes. Generally, cognitive flexibility has been repeatedly linked to the activity of the prefrontal and posterior parietal cortices. The specific regions involved in cognitive flexibility seem to be the prefrontal cortex (PFC) and especially the ventrolateral PFC, dorsal anterior insula (dAI), the inferior frontal junction (IFJ) and posterior parietal cortex (PPC) (Dajani & Uddin, 2015). The role of the lateral PFC has been described in inhibitory control (Anderson & Weaver, 2009; Aron et al., 2014), but it also plays a role in set-shifting or task-switching, where it is important for updating a task rule (Dajani & Uddin, 2015). The IFJ is activated in many cognitive flexibility paradigms and has been suggested to participate in updating the task rules or the task sets (Kim et al., 2012). The dorsal anterior insula and dorsal anterior cingulate cortex (dACC) are part of the salience network that is implicated in directing attention and, during set-shifting, might be necessary for shifting attention to a new set. Other areas responsible for executive functions, like the dorsolateral prefrontal cortex or superior parietal lobule, are also active during cognitive flexibility tasks (Dajani & Uddin, 2015). The PPC is crucial for visual attention (Kim et al., 2012), so it is necessary but not specific to most cognitive flexibility paradigms (Dajani & Uddin, 2015). Recruitment of the lateral and medial PFC and PPC areas in cognitive flexibility tasks has also been found in rodent studies (Birrell & Brown, 2000; Bissonette et al., 2008; Cordova et al., 2014; Fox et al., 2003).

Barbey et al. (2013) analyzed which region may underly selectively cognitive flexibility and identified the right anterior superior temporal gyrus as such. Their results further suggest that cognitive flexibility is associated with activity in areas responsible for several cognitive processes recruited in most cognitive flexibility tasks. Mainly, regions responsible for language processing (Broca's area and left superior temporal gyrus), working memory and spatial processing (left dorsolateral PFC, left inferior and superior parietal cortex, and left superior temporal gyrus) and motor control (left somatosensory and primary motor cortex). Apart from that, studies on rodents, monkeys, and humans have shown that lesions in the orbitofrontal cortex (OFC) can be linked with a reversal deficit, while lesions in the medial/lateral PFC with deficits in ED shifting (Keeler & Robbins, 2011).

Also, subcortical areas, mainly the hippocampus and the dorsal striatum, are involved in cognitive flexibility. Generally, the hippocampus is involved in spatial cognitive flexibility tasks (Stacho & Manahan-Vaughan, 2022), as it has been considered an essential brain structure for navigation (reviewed, for example in Hartley et al., 2014; Moser et al.,

2008). However, the hippocampus is not selectively involved in navigation. It has a general role in memory, which translates into other complex cognitive tasks (Eichenbaum, 2017). In cognitive flexibility, the hippocampus and striatum have been found to contribute to probabilistic learning (Dickerson et al., 2011). Specifically, the striatum has a role in reinforcement learning (Costa et al., 2016; Cox & Witten, 2019), especially in learning the value of the stimuli (Rothenhoefer et al., 2017), and the ventral hippocampus is important for feedback learning (Dickerson & Delgado, 2015). Damage to the hippocampus and basal ganglia have been associated with worse performance in probabilistic reversal task (Myers et al., 2006; Shohamy et al., 2009). However, Shohamy and colleagues (2009) showed that patients with the basal ganglia damage due to Parkinson's disease were able to „solve" the reversal phase by opting for a new cue. Although they had problems with learning a new response to the already known cue, they could learn a new response to a new cue. Therefore, unlike patients with the bilateral hippocampal damage, they opted for a new cue more often when given the opportunity to do so, and this action improved their overall performance. On the other hand, patients with bilateral hippocampal damage had not only more perseverative errors but also failed to learn a new cue and effectively respond to changing conditions. The hippocampus possibly underlies learning of the task structure, including temporal-based anticipatory strategies related to reversal occurrences (Vilà-Balló et al., 2017), which may at least partially explain why patients with hippocampal damage perform worse in the probabilistic reversal learning tasks. The suggested neurobiological mechanism is the hippocampal long-term depression (Dong et al., 2013; Mills et al., 2014), which underlies pattern separation and, in a way, also inhibition of old information, enabling learning a new one (Stacho & Manahan-Vaughan, 2022). The striatum has been linked mainly to establishing a new strategy in reversal and set-shifting tasks (Prado et al., 2017). The dorsomedial striatum is implicated in reversal learning without disrupting the initial learning per se. For example, bilateral inactivation of the dorsomedial striatum with local anesthetic bupivacaine impaired reversal learning in the plus-maze with more regressive errors without disrupting acquisition learning (Ragozzino et al., 2002).

In other studies, authors looked at the connectivity of various regions and their role in cognitive flexibility. For example, Vatansever et al. (2016) found that fewer errors in ID/ED tasks were associated with greater resting state functional connectivity between the default mode network (DMN) and the ventromedial striatopallidum. In another study, authors found that higher variability of dynamic functional connectivity between the frontoparietal network and the DMN is related to better cognitive flexibility measured by the

Stroop test. On the other hand, increased variation in dynamic functional connectivity between these two networks during the resting state was related to poorer cognitive flexibility (Douw et al., 2016). Barbey et al. (2013) described that cognitive flexibility is significantly affected by lesions in white matter sectors of the left hemisphere, including the superior longitudinal/arcuate fasciculus that connects frontal, temporal and parietal cortices. Kim et al. (2012) further suggested that a stronger connection between the IFJ and the PPC may be associated with shorter switching times. The hippocampus and its connections to the PFC are important for a spatial version of reversal learning (Avigan et al., 2020). Specifically, the connection between the ventral hippocampus and the OFC seems to play a significant role, as contralateral lesions in these areas significantly impaired the early stages of reversal in the MWM (Thonnard et al., 2021).

1.3.1 Role of neurotransmitters and neuromodulators in cognitive flexibility

Executive functions are often impaired in conditions known for a disrupted dopaminergic system, like Parkinson's disease or schizophrenia (Lange et al., 2018; Wobrock et al., 2009), so a lot of evidence points toward the role of dopamine in cognitive flexibility (Klanker et al., 2013). However, also other neurotransmitters are probably involved in optimal cognitive flexibility functioning.

Dopamine

Intact dopamine neurotransmission, especially in the striatum and PFC, is associated with better performance in several cognitive flexibility tasks, like the WCST or task-switching (Hsieh et al., 2010). Dopamine seems to influence set-shifting performance mainly through D2 receptors in the striatum and anterior cingulate cortex (ACC) and D1 receptors in the PFC (reviewed in Klanker et al., 2013). Takahashi et al. (2008) described a positive linear correlation between D1 receptor binding in the PFC and the WCST performance and a U-shaped relationship between the level of D1 receptor expression in the PFC and the WCST results. They also found a positive linear correlation between the WCST results and D2 receptor binding in the hippocampus but not in the PFC. D1 receptors in the PFC have been linked to (spatial) working memory (Seamans & Yang, 2004; Vijayraghavan et al., 2007), which is recruited virtually in all cognitive flexibility tasks, so their role in cognitive flexibility is not surprising. In another study, authors found that blockade of D1 receptors in the medial prefrontal cortex (mPFC) and OFC (both systemic and local) and local blockade

of dopamine D2 receptors in the mPFC worsened the performance in a behavioral flexibility test in the Skinner box (Winter et al., 2009).

Furthermore, some studies showed the interaction of genetic variants and treatment with drugs increasing dopamine synaptic availability, like bromocriptine or tolcapone. Dopamine agonist bromocriptine improved performance in human set-shifting tasks, mainly in participants with genetically lower dopamine levels. Pretreatment with selective D2 antagonist sulpiride eliminated the beneficial effect of bromocriptine, which suggest an important role of D2 receptors (van Holstein et al., 2011). Similarly, Apud et al. (2007) found that treatment with catecholamine-*O*-methyltransferase (COMT) inhibitor tolcapone improved ID shifting in the IED test in homozygous participants for valine allele (*val/val* genotype), who have higher COMT activity and consequentially lower concentration of extracellular dopamine levels. In participants with *met/met* genotype and naturally higher dopamine levels, tolcapone worsened the performance, suggesting too low but also too high dopamine levels might impair ID shifting. COMT inhibition by tolcapone also improved set-shifting in rats, although selectively extradimensional phase. Surprisingly, tolcapone did not affect extracellular dopamine levels in rats‘ medial PFC. (Tunbridge et al., 2004). However, there is also evidence of weak (Barnett et al., 2007) or no association between the COMT genotype and the results of several cognitive tests, including the WCST (Barnett et al., 2008). One recent study found an association between the COMT genotype and the WCST performance, but only in participants with lower IQ. Authors suppose that higher IQ may compensate for the potential deficit in cognitive flexibility (Zmigrod & Robbins, 2021), which may partially explain discrepancies between studies.

Other studies looked at dopamine in the striatum. Hsieh et al. (2010) found a negative correlation between the availability of dopamine transporters in the striatum and perseverative errors in the WCST. Darvas and Palmiter (2011) used viral inhibition of dopaminergic signaling in the dorsal or ventral striatum and found a deficit in strategy shifting in mice with impaired dopamine signaling in the dorsal striatum. In a study with rats, dopamine depletion in the dorsomedial striatum by local administration of 6-hydroxydopamine (6-OHDA) impaired reversal learning but not the initial acquisition phase (O’Neill & Brown, 2007). Similarly, Tait et al. (2017) showed that rats with dopamine depletion in the dorsomedial striatum were significantly worse in the reversal stage of set-shifting. Rats with lesions in the subthalamic nucleus (STN) caused by injections of ibotenic acid made more errors in the reversal and ID shifting as well as in initial acquisition. Surprisingly, rats with lesions in both areas were not different from the control group. Here

comes to light the intertwined system of brain neurotransmitters. Acute dopaminergic depletion in the striatum seems to increase striatal (but not cortical) extracellular glutamate levels, while chronic dopaminergic depletion decreases striatal glutamate levels (Caravaggio et al., 2016). Dopaminergic depletion in the striatum and lesion of the STN may hypothetically level up the imbalance between the direct and indirect pathways caused by only one of them.

Apart from the dorsal striatum, dopamine in the nucleus accumbens (NAc) may also be important for reversal learning. Optogenetic silencing, but not stimulation, of ventral tegmental area (VTA) dopaminergic inputs to the NAc impaired early reversal, although not overall performance (Radke et al., 2019). Contrarily, in the study with rats, stimulation of D2 receptors by D2/D3 agonist quinpirole injected into the NAc impaired reversal learning in the Skinner box (Haluk & Floresco, 2009). Again, possibly suggesting not only depletion but also excessive activation of the dopaminergic system might be detrimental to cognitive flexibility. On the other hand, some studies conclude that although intermediate dopamine levels correlate with better working memory, higher dopamine levels correlate with better performance in cognitive flexibility tests[1] (Fallon et al., 2015; Fang et al., 2019).

Noradrenaline

Noradrenergic projections to the prefrontal cortex have been implicated in executive functions (Arnsten & Li, 2005; Holland et al., 2021). Notably, 6-OHDA lesions of the dorsal noradrenergic ascending bundle leading to selective depletion of noradrenaline in the mPFC resulted in impairment in extradimensional shifting (Tait et al., 2007). Similarly, other studies found that rats with noradrenergic depletion in the mPFC performed worse in ED shifting but not in other phases of the task (McGaughy et al., 2008; Newman et al., 2008). Also, optogenetic silencing of locus coeruleus resulted in impaired reversal learning and ED shifting (Janitzky et al., 2015). Furthermore, the administration of atomoxetine, a selective noradrenaline reuptake inhibitor, ameliorated the performance of lesioned rats but worsened the ED shifting of the control group. Therefore, even too high noradrenaline levels might be detrimental to ED shifting. ED shifting was also improved by an agonist of alfa-2 adrenergic receptors, guanfacine, in abstaining participants with cocaine dependence (Fox et al., 2015). Although, in other studies with healthy subjects, there was no effect of alfa-2 adrenergic agonists (Choi et al., 2006; Müller et al., 2005). Also, stress-related impairments of cognitive

[1] It should be noted, that both studies were conducted on participants with Parkinson's disease, who may have alterations in neurotransmitter system compared to healthy people.

flexibility were remediated by an antagonist of beta-adrenergic receptors, propranolol (Alexander et al., 2007), although in animal studies, propranolol did not affect cognitive flexibility (Hecht et al., 2014). Interestingly, propranolol was beneficial for participants experiencing more difficulties with the task or in more difficult trials (Campbell et al., 2008).

Serotonin

Serotonin is implicated in emotional regulation and various cognitive functions, including response inhibition (Cools et al., 2008), decision-making, or positive/negative feedback processing (Chamberlain et al., 2006; Rygula et al., 2015). Due to its projections to the PFC and OFC, it has also been studied in the relationship to cognitive flexibility. Reversal learning has been impaired after the depletion of serotonin precursor tryptophan in healthy participants (Kanen et al., 2021). However, some studies showed no effect of tryptophan depletion on cognitive flexibility (Talbot et al., 2006; van der Plasse & Feenstra, 2008). In one study, the depletion of serotonin in the PFC disrupted reversal learning but not extradimensional set-shifting in monkeys (Clarke et al., 2005). On the other hand, rats with serotonin transporter knockout had better performance in the ED shifting (Brigman et al., 2010; Nonkes et al., 2012), suggesting higher serotonin concentration may improve cognitive flexibility. In another study using a probabilistic learning task, the authors found no effect of tryptophan depletion on reversal errors. Still, it significantly increased negative feedback sensitivity measured by a shift towards generally non-rewarded stimuli after misleading negative feedback (Thirkettle et al., 2019). Negative feedback sensitivity in healthy human subjects has also been impaired by acute administration of escitalopram (30mg), and participants who received escitalopram needed more trials to reach the criterion (Chamberlain et al., 2006). Interestingly, there might be distinct effects of acute escitalopram administration on different cognitive domains. While it seems to improve inhibitory control, it impairs extradimensional set-shifting and probabilistic learning by increasing sensitivity to negative feedback (Skandali et al., 2018). Furthermore, acute and chronic administration of selective serotonin reuptake inhibitors (SSRIs) seems to have the opposite effect, as a single dose of escitalopram decreased serotonin concentration in serotonergic projection areas, including the PFC (Nord et al., 2013).

Notably, Groman and colleagues described a relationship between serotonin in the orbitofrontal cortex, dopamine in the putamen and reversal learning in monkeys. When the dopamine levels in the putamen were low, better performance in reversal learning was associated with higher OFC serotonin levels, but when the putamen dopamine levels

increased, better performance was associated with lower OFC serotonin levels (Groman et al., 2013). Also, specific types of serotonergic receptors may have different roles in different cognitive flexibility tasks. The set-shifting task was enhanced by an administration of 5-HT6 antagonists SB-271046 and SB-399885-T (Hatcher et al., 2005; Rodefer et al., 2008), 5-HT7 antagonist SB-269970 (Hrnjadovic et al., 2021; Nikiforuk, 2012) and atypical antipsychotic sertindole, that also has a high affinity to 5-HT6 receptors (Nikiforuk & Popik, 2012; Rodefer et al., 2008). On the other hand, 5-HT6 agonist WAY181187 also enhanced ED shifting (Burnham et al., 2010). 5-HT2A antagonists seem to improve strategy switching (Baker et al., 2011), while 5-HT2C antagonists seem to improve spatial reversal learning without the necessity to switch the strategy (Boulougouris et al., 2008). However, apart from their serotoninergic activity, 5-HT6 antagonists also seem to increase extracellular glutamate (Dawson et al., 2000; Mørk et al., 2009). Sertindole increases extracellular dopamine, acetylcholine and glutamate levels in the PFC (Mørk et al., 2009), and WAY181187 increases extracellular GABA levels (West et al., 2009). The results of mentioned studies again point toward the interplay between several neurotransmitter systems rather than an exclusive role of one of them.

Glutamate

Glutamate has been considered to have a leading role in synaptic plasticity (Barnes et al., 2020; Valtcheva & Venance, 2019) and, as such, has also been studied in the context of cognitive flexibility. For example, Ding and colleagues tested rats in a nose-poke set-shifting task and found that infusion of NMDA receptor antagonist AP5 to the NAc shell impaired reversal learning by increasing regressive errors. In contrast, injections to the NAc core increased perseverative errors and injections to the dorsomedial and dorsolateral striatum impaired ID but not ED shifting. On the other hand, the blockade of AMPA receptors in the striatum had no effect on set-shifting performance (Ding et al., 2014). Consistently, systemic application of NMDA antagonists PCP, ketamine and MK-801 caused reversal learning impairment in rats (Abdul-Monim et al., 2007; Floresco et al., 2009; Idris et al., 2009; van der Meulen et al., 2003). Also, mice with deficient vesicular glutamate transporter 1 (VGLUT1) had impaired hippocampal long-term potentiation (LTP) in the CA1 region of the hippocampus, as well as spatial reversal in the MWM and visual touchscreen reversal task (Balschun et al., 2010; Granseth et al., 2015). Furthermore, mice with glutamate subunit GluN2A brain-wide knockout performed worse in the ED shifting in a maze but not in a reversal in the touchscreen visual task (Marquardt et al., 2014).

Furthermore, cognitive flexibility is often impaired in patients with schizophrenia (e.g., Everett et al., 2001; Singh et al., 2017), where altered glutamatergic neurotransmission is implicated (Uno & Coyle, 2019).

Gamma-aminobutyric acid (GABA)

GABA is a primary inhibitory neurotransmitter in CNS. GABAergic parvalbumin-expressing interneurons (PVIs) in the prefrontal cortex are implicated in cognitive impairment in conditions like schizophrenia, possibly by their involvement in generating gamma oscillations (Dienel & Lewis, 2019). Also, reduced density of PVIs has been found in patients with schizophrenia post-mortem (Kaar et al., 2019) as well as lower levels of GAD67 mRNA (Hashimoto et al., 2003), which is an isoform of glutamic acid decarboxylase, that catalyzes glutamate to GABA. Recent genome-wide association studies have found a link between altered GABAergic functioning and deficits in executive functions (Hatoum et al., 2023). Furthermore, a study on healthy older adults linked a decline in frontal GABA levels to lower scores in cognitive screening with the Montreal Cognitive Assessment (Porges et al., 2017). In another study, GABA levels in the dorsal ACC were significantly associated with the WCST performance (Marenco et al., 2018). On the other hand, supplementation of synthetic GABA in healthy participants was linked to worse results in the Switcher task, selectively impairing the switching aspect of cognitive flexibility (Lim & Aquili, 2021)[2].

Similarly, in animal studies, inhibition of PVIs in the prefrontal cortex of PV-Cre mice resulted in a deficit in spontaneous alternation in the Y-maze and reversal in the MWM but not in social preference and recognition test in the three-chamber, suggesting PVIs might be specifically implicated in cognitive functions, like working memory and cognitive flexibility (Murray et al., 2015). Another study showed that only a 30% loss of cortical PVIs resulted in selective impairment in reversal learning in the digging tasks and cued learning in the MWM (Martins et al., 2011). A significantly lower number of PVIs in the OFC and striatum was found in B6.129-*Plaur*$^{tm1/Mlg}$/*Plaur*$^{tm1/Mlg}$ mice, who needed more trials to criterion in the reversal part of the set-shifting digging task compared to wild-type or different transgene mice that had no change in PVIs number (Bissonette et al., 2010). Also, myelination defect in PVIs was associated with impaired spatial working memory tested in

[2] However, it is still unclear, whether GABA can cross the blood brain barrier, so the results could be influenced by the effects on peripheral or perhaps enteric nervous system (Boonstra et al., 2015).

the T-maze and impaired ED shifting in apomorphine-susceptible (APO-SUS) rats[3]. The reversal was not impaired initially but only after several reversals (Maas et al., 2020). Furthermore, impaired reversal learning after $GABA_A$ inhibition was also found in drosophila flies (Ren et al., 2012).

Acetylcholine

Acetylcholine has an important role in several cognitive processes, especially in memory, learning and sustained attention (Mineur & Picciotto, 2021). In relation to cognitive flexibility, mainly cholinergic signalization in the striatum and prefrontal cortex have been studied. For example, blockade of cholinergic muscarinic receptors in the dorsomedial striatum in rats with local injections of scopolamine (at a dose of 8 μg) spared acquisition learning but impaired reversal learning in the cross maze leading to a higher number of regressive errors (Ragozzino et al., 2002). Also, modulation of muscarinic M2 autoreceptors by injection of oxotremorine sesquifumurate into the dorsomedial striatum impaired reversal learning and reduced acetylcholine output, while M2 muscarinic receptor antagonist AF-DX-116 reversed this effect (Ragozzino et al., 2009). Similarly, mice with genetically reduced vesicular acetylcholine transporter (VAChT) protein expression in the forebrain, and thus reduced acetylcholine release in the PFC, hippocampus, and striatum, had impaired spatial reversal in the MWM (Al-Onaizi et al., 2017) and an impaired reversal in the touchscreen visual discrimination and reversal task (Kolisnyk et al., 2013). Furthermore, positive allosteric modulation of nicotinic alfa 7 acetylcholine receptors (α7-nAChRs) and inhibition of acetylcholinesterase by administration of galantamine enhanced the performance in ED shifting in the set-shifting digging task in rats (Nikiforuk et al., 2015). In another study, inhibition of acetylcholinesterase with Donepezil improved reversal learning in the water T-maze in male BTBR *T+tf/J* mice – a rodent model relevant to autism spectrum disorder (Karvat & Kimchi, 2014). The spatial reversal in the MWM was also facilitated by the activation of muscarinic M1 receptors in the CA1 region of the hippocampus (Xiong et al., 2019).

However, striatal cholinergic interneurons have been found to co-release glutamate (Higley et al., 2011) and cholinergic neurons in basal forebrain co-release GABA together with acetylcholine (Saunders et al., 2015), which may complicate determining specific contributions of acetylcholine, glutamate and GABA to cognitive flexibility. Based on

[3] Apomorphine susceptible (APO-SUS) rats are rats with high response to dopamine agonist apomorphine and are a well-characterized animal model relevant to schizophrenia (Ellenbroek et al., 1995).

specific genetic models, such as VAChT knockout, we can conclude that acetylcholine transmission in the dorsomedial striatum and prefrontal cortex is indeed crucial for learning new strategies and inhibition of previously learned ones (Prado et al., 2017) and in the hippocampus for spatial reversal learning (Al-Onaizi et al., 2017).

1.4 Impairment of cognitive flexibility in psychiatric disorders

Impaired cognitive flexibility has been described in several psychiatric disorders. Patients with schizophrenia often have worse results in the WCST compared to healthy controls, but there is a discrepancy in the exact type of mistakes among studies. Several studies showed patients with schizophrenia made more perseverative errors (Bustini et al., 1999; Haut et al., 1996; Morice, 1990; Morice & Delahunty, 1996; Wobrock et al., 2009), and in some studies, they also completed fewer categories or needed more time to complete them (Morice, 1990; Bustini et al., 1999). In other studies, they made more overall mistakes but not specifically perseverative errors (Wilmsmeier et al., 2010). Bustini et al. (1999) found a positive correlation between delusions and perseverative errors in the WCST, so differences in symptoms and illness severity may at least partially explain the divergent results. However, patients with schizophrenia had worse performance also in other tests of cognitive flexibility, like the CANTAB IED task (Ceaser et al., 2008; McKirdy et al., 2009), the Trail Making Test (Wobrock et al., 2009), its‘ variant the Color Trail Test (Tyburski et al., 2020) and also in a virtual reality task, where only 30% of patients acted flexibly compared to 80% of a control group (Han et al., 2012). A deficit in cognitive flexibility does not seem to occur in the siblings of schizophrenia patients (Ceaser et al., 2008) or in the first episode patients when controlled for spatial working memory deficits (Pantelis et al., 2009). Yet, patients with chronic schizophrenia had worse results in the IED task that could not be explained only by deficits in spatial working memory (Pantelis et al., 2009). Also, in the study of Leeson et al. (2009), worse performance in ED shifting disappeared after controlling for IQ, but impairment in reversal was still significant. In another study, schizophrenia patients with above-average IQ had almost comparable performance to the control group in the IED task (Ceaser et al., 2008), suggesting higher intelligence may help to compensate for the deficit. Overall, cognitive flexibility seems to be decreased in a majority of schizophrenia patients. However, also other variables, such as IQ, (spatial) working memory, medication, prevailing symptomatology, length, and course of the disease, together with methodological differences between studies, may influence the results. Interestingly, chronic schizophrenia patients have worse shifting abilities compared to first-episode patients, although further deterioration during the illness was not confirmed (Pantelis et al., 2009; Tyson et al., 2004).

A similar deficit as in schizophrenia patients was also described in patients with bipolar disorder (Fleck et al., 2008; McKirdy et al., 2009; Morice, 1990; Robinson et al.,

2006) and severe depression with psychotic features (Rady et al., 2012). Although, in a study by Mak et al. (2018), bipolar patients with predominantly depressive states were less impaired than those with unipolar depression. Also, a meta-analysis by Wagner and colleagues (2012) suggests impaired cognitive flexibility measured by the TMT B in patients with unipolar depression. Patients with anorexia nervosa and other eating disorders also performed worse in the WCST (Duchesne et al., 2010; Tchanturia et al., 2012; Westwood et al., 2016).

Impaired cognitive flexibility has been further suggested in obsessive-compulsive disorder (OCD) and autism spectrum disorder (ASD), where it is one of the hallmark features. Patients with OCD had worse performance in several cognitive flexibility tests, including the WCST (Bannon et al., 2006; Cavedini et al., 2010; Lawrence et al., 2006; Snyder et al., 2015; Zhang et al., 2015), the CANTAB IED task (Olley et al., 2007; Watkins et al., 2005), the TMT B (Henry, 2006; Moritz et al., 2002) and the Object Alternation Test (Shin et al., 2014; Snyder et al., 2015). Also, children and adolescents with OCD had more errors and fewer completed categories in the WCST (Shin et al., 2008). Interestingly, the deficit in the WCST, including a higher number of perseverative responses, was also shown in a subclinical population (Kim et al., 2009) and healthy siblings of OCD patients (Cavedini et al., 2010). On the other hand, in the study by Zhang et al. (2015), OCD patients and their siblings had normal performance in the WCST. Also, in several other studies, authors found no difference between OCD and healthy control group in the WCST (Kodaira et al., 2012; Kohli et al., 2015) and in the study by Delorme et al. (2007), relatives of OCD patients had comparable results to control group in the TMT. Again, different results might be influenced by variance in the research sample, research methods and other confounding variables. For example, covariation with the Wechsler Adult Intelligence Scale results showed that patients with OCD only completed fewer categories, while other deficits in the WCST were no longer significant (Bucci et al., 2007). Similarly, when controlling for education, patients with OCD needed more time for the answer in the Object Alternation Test but had no other deficits. This suggests a lower psychomotor pace but not necessarily flexibility deficits (Gross-Isseroff et al., 1996). In another study, the authors looked at the effect of insight and found that the group with bad insight was more impaired, especially in the WCST and the TMT (Tumkaya et al., 2009). Also, patients with different prevailing dimensions might have various cognitive impairments. Some studies suggest worse cognitive flexibility in patients with predominantly checking OCD subtype (Leopold & Backenstrass, 2015; Omori et al., 2007).

Behavioral rigidity is one of the key clinical features of ASD, and so many researchers examined cognitive flexibility in this population. Some studies found a positive correlation between repetitive behavior and perseverative errors in the WCST and ED part of the IED task in children, adolescents, and adults with ASD (South et al., 2007; Yasuda et al., 2014; Yerys et al., 2009). On the other hand, some other studies found no difference between ASD and the control group. Performance in the WCST was not impaired in adults with ASD (Di Sarro et al., 2022), as well as in children with lower IQ (Lung & Bertone, 2021). Also, in the study of Wolff and colleagues, adolescents with ASD performed similarly to the control group. Interestingly, increasing working memory load impaired performance in the repetitive trials but not the switching (Wolff et al., 2018). Likewise, in task switching with emotional faces, children with ASD did not show cognitive flexibility deficits (de Vries & Geurts, 2012). Therefore, some researchers tried to address this discrepancy between an apparent inflexibility in the daily life of people with ASD and inconsistent results of studies. Van Eylen et al. (2011) argued that people with ASD have worse results, specifically in tests with a low degree of explicitly provided task instructions, like the WCST, while in tasks with a higher percentage of explicit instructions, they may not have such problems with switching. It is also possible that impaired performance in cognitive flexibility tests may be partially explained by deficits in attention, as approximately 40-50% of patients with ASD have comorbid attention deficit hyperactivity disorder (Geurts et al., 2009). Generally, it seems that patients with ASD have impaired cognitive flexibility, but it emerges only under specific conditions, e.g., lack of explicit instructions or less predictable changes. Usually, there is also higher variability in the sample of patients compared to the control group, making the results harder to interpret.

Results of the before-mentioned studies imply that impairments in cognitive flexibility have been observed in various psychiatric disorders. Notably, inflexibility in beliefs, thinking style, and specific cognitive biases have been suggested by some researchers to be an important factor in the development and maintenance of delusions in psychotic disorders, but also of depressive symptoms, post-traumatic stress disorder, obsessive-compulsive disorder and so on (Davis et al., 2016; Jelinek et al., 2016; Miegel et al., 2021; Moritz & Woodward, 2007). However, cognitive inflexibility has been mainly associated with three psychiatric and neurodevelopmental disorders: schizophrenia, obsessive-compulsive disorder, and autism spectrum disorder. Therefore, the following parts of the thesis will be focused selectively on these three disorders.

1.5 Cognitive flexibility in rodent models of selected psychiatric disorders

Animal models are an essential tool for studying pathological processes. However, it is very challenging to model something so complex as a psychiatric or neurodevelopmental disease. It is almost impossible to design an animal model that would reflect all behavioral and neurobiological manifestations seen in humans. Furthermore, psychiatric disorders often manifest in a variety of different symptoms. Therefore, we should rather talk about animal models relevant to a particular disease or, even more precisely, to a specific symptom, such as compulsivity, perseveration, inflexibility, or social interaction impairment. However, even with careful interpretation, the validity of the animal model might be hard to assess based only on behavioral observation. For example, rituals in OCD are most often provoked by anxiety caused by obsessions and, as such, are phenomenologically distinct from other repetitive behaviors (e.g., tics). It is, therefore, hard to determine if repetitive behaviors in animal models relevant to OCD represent true compulsions (Abramowitz et al., 2011).

What constitutes an animal model with satisfying validity depends partially on the research purpose (e.g., examining etiology or preclinical drug evaluation), but generally, three main types of validity should be considered: face, construct, and predictive. Face validity refers to a behavioral similarity between an animal model and symptoms of a human condition. Construct validity is based on the involvement of brain structures, neurobiological mechanisms, or pathophysiological processes implicated in human disease. Predictive validity is based on the effectiveness of medication used to treat the condition in humans (Alonso et al., 2015).

The key symptoms of schizophrenia, OCD, and ASD and corresponding behavioral tests used to assess the symptoms in rodent models are described in Table 1.

	SYMPTOMS	RODENT BEHAVIORAL TESTS
Schizophrenia	**POSITIVE**	
	Psychomotor agitation	Locomotor activity in the open field
	Sensitivity to psychotomimetic drugs	Locomotor response to amphetamine or non-competitive NMDA receptor agonists
	NEGATIVE	
	Social withdrawal	Social interaction in the open field, social preference and social novelty in the three-chamber test
		Home-cage social interaction
		Altered social dominance in the tube test
		The resident-intruder test
	COGNITIVE	
	Working memory deficits	Alternation in the Y-maze or the T-maze
		The 8-arm radial maze working memory task
	Deficits in sensorimotor gating and associative learning	Prepulse inhibition
		Latent inhibition
	Deficits in executive functions (impaired reversal learning/set-shifting, deficits in attention and impulse control)	Set-shifting or reversal
		The 5-choice serial reaction time test
	General cognitive deficit (spatial learning, working memory, long-term memory)	The Morris Water Maze (MWM), the Active Allothetic Place Avoidance (AAPA), the 8-arm radial maze, an operant task, etc.
OCD	**COMPULSIVE BEHAVIOR**	
	Repetitive movements, stereotypic motor activity pattern	Repetitive jumping, running, grooming, hair pulling etc.
	Compulsive checking	Checking of objects in the open field
	Increased locomotion	Locomotion in the open field
	Other	Marble burying
	AFFECTIVE	
	Increased anxiety	The elevated plus maze (EPM)
	DEFICITS IN EXECUTIVE FUNCTIONS	
	Impaired set-shifting or reversal learning	Set-shifting or reversal
	Working memory deficits	Alternation in the Y-maze or the T-maze
	Impaired inhibition, perseveration	Perseveration in a reversal/set-shifting task, the Y-maze or T-maze
ASD	**DECREASED SOCIABILITY AND INTERACTION**	
	Impaired communication	Ultrasonic vocalization (e.g. isolation-induced vocalization in pups or vocalization of adult males responding to female urinary pheromones)
		Olfactory communication, olfactory habituation/dishabituation to social odors
		Social transmission of food preference
	Decreased interaction and social preference	Social approach and preference in the three-chamber, social interaction in the open field
	REPETITIVE BEHAVIOR	
	Repetitive movements	Repetitive jumping, running, grooming, hair pulling etc.
	Insistence on sameness, perseveration	Neophobia, perseveration in the Y-maze, T-maze or a reversal task
	COGNITIVE DEFICITS	
	Impairments in learning ability, working memory, long-term memory	Spatial learning and memory in the MWM, the AAPA or the 8-arm radial maze, working memory in the Y-maze/T-maze, learning in the operant task, etc.

Table 1: Rodent behavioral tests relevant to symptoms of schizophrenia, OCD, and ASD (Adapted from (Ahmari, 2016; Powell & Miyakawa, 2006; Silverman et al., 2010).

1.5.1 Rodent models relevant to schizophrenia

Schizophrenia is a severe, often chronic psychiatric disease characterized by a variety of symptoms that can be classified as positive, negative, and cognitive. Positive symptoms include delusions and hallucinations, but also psychomotor agitation or higher responsivity to psychostimulants. Negative symptoms include changes in mood, social withdrawal or loss of motivation and cognitive symptoms, for example, deficits in working memory or

executive functions (McCutcheon et al., 2020). Generally, multiple factors are thought to play a role in schizophrenia development. Schizophrenia is suggested to have a strong genetic component, as twin studies show high heritability liability of around 81% (Sullivan et al., 2003). However, also other risk factors have been described, such as early life stress, childhood trauma (Anglin et al., 2008; Bonoldi et al., 2013), or adversity during development, including maternal infection and obstetric complications (Brown, 2012; Davies et al., 2020).

Several processes have been described as possible underlying causes on a neurobiological level. Specifically, aberrant pruning and network reorganization during adolescence has been described in patients with schizophrenia. Other studies point towards a lower percentage of gray matter (Hulshoff Pol et al., 2002) and reduced volume of the hippocampus, amygdala, thalamus, nucleus accumbens and larger pallidum and lateral ventricles (Feinberg, 1982; van Erp et al., 2016). Furthermore, postmortem studies found a significantly lower density of GABAergic parvalbumin-positive interneurons in the frontal cortex of schizophrenia patients together with slightly lower levels of parvalbumin mRNA (Kaar et al., 2019) and a glutamate decarboxylase 67 - an enzyme involved in GABA synthesis (Guidotti et al., 2000), which indicates impaired inhibitory processing.

PVIs have been suggested to play a critical role in generating gamma oscillations. Gamma oscillations are high-frequency oscillations (30-200 Hz) that are involved in several mental processes, mainly in working memory (Lundqvist et al., 2018), emotional processing (Headley et al., 2021) or locomotion (Guerra et al., 2020, 2022). Importantly, aberrant gamma oscillations and impaired theta-gamma coupling during working memory have been described in patients with schizophrenia (Barr et al., 2017; Basar-Eroglu et al., 2007; Minzenberg et al., 2010; Tanaka-Koshiyama et al., 2020).

Furthermore, dysregulation in neurotransmitter systems, mainly dopaminergic and glutamatergic, has been suggested as the leading underlying cause of the disease. Dopaminergic neurons are a target of many antipsychotics. Specifically, mesostriatal dopamine neurons have a significant role in distinguishing salient and non-salient stimuli and therefore have been thought to play a role mainly in positive symptoms of schizophrenia (Kapur, 2003). Simultaneously, hypofunction of NMDARs and excessive glutamate release is suggested to evoke cognitive and negative symptoms (Mei et al., 2018), as NMDAR agonists, such as ketamine or phencyclidine, produce schizophrenia-like symptoms in healthy adults (Krystal et al., 1994) as well as in animal models (Frohlich & Van Horn, 2014; Mouri et al., 2007).

Genetic models

Genetic models relevant to schizophrenia are based on the findings of high heritability (Sullivan et al., 2003). Common, rare and de novo mutations, together with environmental factors, were found to increase susceptibility to schizophrenia (Greenwood et al., 2019). One of the first genes implicated in schizophrenia was a disrupted in schizophrenia 1 (DISC1). DISC1 is a synaptic protein involved in neuronal development, mainly synaptogenesis, neuronal migration and synaptic plasticity (Jaaro-Peled, 2009). Several transgenic mice with mutations resulting in partial DISC1 loss have been developed. They were shown to manifest behavioral and physiological characteristics similar to those found in schizophrenia, such as locomotor hyperactivity, subtle deficits in sensorimotor gating measured by prepulse inhibition (PPI), cognitive deficits, enlarged lateral ventricles, and reduced cortical thickness (Hikida et al., 2007; Pletnikov et al., 2008). Other genetic rodent models are based on mutations or knockouts that target dopaminergic or glutamatergic neurotransmission, such as dopamine transporter knockout, which leads to persistently elevated dopaminergic tone (Ralph et al., 2001), COMT-Val polymorphism models (described in Chapter 3.1.1), or GluN2A knockouts. Other rodent genetic models relevant to schizophrenia are based, for example, on changes in neuregulin-1 (NRG1)[4] (O'Tuathaigh et al., 2010), dysbindin-1[5] (Talbot, 2009), reelin[6] (Tueting et al., 2006), apomorphine (APO-SUS rats) (Ellenbroek et al., 1995)[7] or 22q11.2 microdeletion[8] (Sumitomo et al., 2018).

Although schizophrenia-like impairments, such as deficits in working memory, impaired prepulse inhibition, and hyperactive locomotion, have been described in many of the higher-mentioned genetic models (reviewed in van den Buuse, 2009), cognitive

[4] NRG1 is a trophic growth factor that contains epidermal growth factor domain and its receptors are ErbB. NRG1-ErbB4 signaling is involved in the developement of nervous system (e.g. neuronal migration, axon guidance, myelination, synaptic formation) (Mei & Xiong, 2008).

[5] DTNBP1 gene, that encodes dysbindin-1 is considered one of schizophrenia susceptible genes. Disbindin-1 is involved in stability of muscle fibres and in the CNS contributes to mantaining the structure and physical stability of synaptic membrane (Wang et al., 2017). Deficiency in disbindin-1 complex therefore impacts synaptic homeostasis and efficacy (Dickman & Davis, 2009).

[6] Reelin is a glycoprotein important for cortical development that modulates synaptic function in adults (Ishii et al., 2016). Reelin-deficient mice have inverted cortical layers (Sekine et al., 2014) and reelin mRNA expression is significantly reduced in the PFC cortex and hippocampus of patients with schizophrenia (Eastwood & Harrison, 2006).

[7] Apomorphin is non-selective dopamine agonist and apomorphin susceptible rats (APO-SUS) show behavioral features similar to schizophrenia (impaired prepulse inhibition, latent inhibition and amphetamine sensitivity, (Ellenbroek et al., 1995; Ellenbroek & Cools, 2002).

[8] 22q11.2 deletion syndrom (22q11DS) is a genetic syndrome with variable clinical symptoms. Around 1% of patients with schizophrenia have this syndrom (Bassett & Chow, 2008), but around 30% of patients with 22q11DS develop schizophrenia (Qin et al., 2020).

flexibility has not been addressed in many studies. Papaleo and colleagues (2008) showed disrupted extradimensional shifting in COMT-Val transgenic mice with higher COMT activity, while mice with COMT knockout didn't complete the task, possibly due to higher anxiety levels. In another study, extradimensional shifting was impaired in mice with knockout of GluN2A type of NMDA receptors (Marquardt et al., 2014). Similarly, in a Df(h22q11)/+ mice model of 22q11.2 microdeletion, the transgenic mice were significantly worse in ED shifting compared to the wild-type control group (Tripathi et al., 2020). Also, *LgDel* mice (another model of 22q11 deletion) were impaired in reversal learning and completed the task more slowly (Meechan et al., 2015). Surprisingly, in another study, Df(h22q11)/+ mice had better reversal learning results than the control group (Nilsson et al., 2016). Those results may reflect general cognitive impairments because lower IQ is often part of the clinical manifestation of this syndrome. However, interindividual differences were described (Zhao et al., 2018), which may explain the discrepancies. Neuregulin 1 heterozygous mice had worse performance in reversal learning in the MWM, mainly on the first day of reversal (Clarke et al., 2017). Cognitive inflexibility has also been described in APO-SUS rats and linked to decreased myelination of PVIs in the mPFC (Maas et al., 2020).

Pharmacologically induced models

Pharmacological models are based on findings that drugs increasing dopaminergic neurotransmission (e.g., amphetamine), serotoninergic psychedelics (LSD or psilocybin), and noncompetitive NMDA antagonists (especially phencyclidine (PCP), dizocilpine (MK-801) or ketamine), produce schizophrenia-like symptoms in both humans and animals (Featherstone et al., 2007; Frohlich & Van Horn, 2014; Javitt et al., 2012; Marona-Lewicka et al., 2011; Moghaddam & Jackson, 2003; Tylš et al., 2014). In animal models, a variety of symptoms related to schizophrenia has been described, such as hyperlocomotion (Kalinichev et al., 2008; Usun et al., 2013; Schlumberger et al., 2010), deficits in sensorimotor gating tested by prepulse inhibition (Geyer et al., 2001) and glutamatergic models also show deficits related to negative symptoms, especially social withdrawal (Qiao et al., 2001; Rung et al., 2005; Sams-Dodd, 1995) and cognitive impairments (Moghaddam et al., 1997; Wiley et al., 2003).

Notably, deficits in cognitive flexibility have been described in pharmacological models. Extradimensional shifting was impaired in the set-shifting digging task after acute administration of PCP, amphetamine, as well as a higher dose of ketamine (10mg/kg) in rats (Egerton et al., 2005; Featherstone et al., 2008; Gastambide et al., 2013; Nikiforuk et al.,

2010). In one study, also reversal stage was impaired in rats after acute PCP administration (Gastambide et al., 2013), and acute administration of MK-801 impaired the performance of rats in the MWM and the AAPA (Lobellova et al., 2013). Furthermore, the administration of ketamine for ten days caused deficits in ED shifting in rats, and the impairment was ameliorated by the administration of atypical antipsychotics sertindole and quetiapine (Nikiforuk & Popik, 2012). Similarly, subchronic and chronic administration of PCP resulted in worse performance in the set-shifting digging task, especially the ED stage (Egerton et al., 2008). PCP also disrupted the performance of rats in an operant reversal task (Abdul-Monim et al., 2003, 2006). In another study, however, authors found disrupted reversal and ED shifting in rats after sensitization with amphetamine but not with PCP (Fletcher et al., 2005).

Also, the administration of PCP in postnatal days (PD) 7, 9 and 11 resulted in impaired extradimensional shifting in adulthood (Broberg et al., 2008). In the same line, rats treated with ketamine in the second postnatal week had more perseverative, regressive and never-reinforced errors in the T-maze set-shifting task tested in adulthood, as well as a reduced number of GABAergic PVIs in the mPFC (Jeevakumar et al., 2015). Also, $GABA_A$ blockade in the prefrontal cortex with bicuculine impaired set-shifting (Enomoto et al., 2011).

Developmental models

Neurodevelopmental rodent models focus on elucidating the etiological factors of schizophrenia. Most wildly used models are based on neonatal ventral hippocampal lesions (NVHL), maternal immune activation (MIA), maternal separation/social isolation, or a combination of several factors in the so-called two-hit (or multiple-hit) model. The NVHL is an established model of schizophrenia that involves the infusion of ibotenic acid into the ventral hippocampus of mice or rats in the first postnatal week, which corresponds to the third trimester in humans. Studies on the NVHL model showed several schizophrenia-like behavioral and physiological features, such as deficits in sensorimotor gating measured by PPI (Joseph et al., 2018; Swerdlow et al., 2013), (spatial) working memory (Brady et al., 2010; Lipska et al., 2002), social interaction (Joseph et al., 2018) and also neurobiological changes, like a reduced expression of dopamine transporter (DAT) mRNA (Lipska et al., 2003). Rats with NVHL were also less flexible in their choices, possibly due to increased PFC excitability (Gruber et al., 2010). In another study, NVHL rats had more perseverative

errors in the operant set-shifting task but a normal performance in a reversal task (Placek et al., 2013).

MIA models are based on epidemiological studies showing that prenatal exposure to maternal infection is a risk factor for the later onset of schizophrenia (Brown & Derkits, 2010). They are induced most often by a single or repeated injection of either bacteria endotoxin lipopolysacharide (LPS) (Baharnoori et al., 2012), viral mimetic polyinosinic:polycytidylic acid (poly(I:C)) (Meyer & Feldon, 2012), the methylazoxymethanol acetate (MAM) (Lodge, 2013) or human influenza virus (Fatemi et al., 2008) to pregnant rats or mice. Another developmental model is maternal separation, based on the finding that early life adversity is a risk factor for schizophrenia (Bonoldi et al., 2013). Models can be further combined, thus creating a multiple-hit model that reflects the multifactorial nature of schizophrenia (Feigenson et al., 2014). Several behavioral and neurobiological characteristics relative to schizophrenia have been described in these developmental models, including changes in sensorimotor gating measured by PPI (Santos-Toscano et al., 2016), latent inhibition of associative learning (Ellenbroek & Cools, 1995; Meyer, Feldon, et al., 2006), deficits in working memory (Santos-Toscano et al., 2016), recognition memory (Potasiewicz et al., 2020), social interaction (Lins et al., 2018; Potasiewicz et al., 2020) and increased response to amphetamine or MK-801 (Lins et al., 2018; Rentesi et al., 2013; Vorhees et al., 2015), as well as changes in the glutamatergic system, asynchronous communication between the mPFC and hippocampus (Dickerson et al., 2010), decreased density of PVIs in the PFC and hippocampus (Lodge et al., 2009) or decreased hippocampal CA1 excitability (Patrich et al., 2016). Importantly, the time of prenatal application was found to cause distinct outcomes. Meyer et al. (2006) compared the application of poly(I:C) on gestational day 9 (GD9), corresponding to the late first or early second trimester in humans, and gestational day 17 (GD17), which should correspond to the third trimester. Treatment with poly(I:C) on GD9, but not GD17, impaired reelin expression in the hippocampus, latent inhibition and decreased spatial exploration. Treatment on GD17 enhanced apoptosis and increased perseverative behavior in the reversal stage in the water T-maze (Meyer, Nyffeler, et al., 2006).

Cognitive flexibility has been examined in several other studies. For example, the administration of poly(I:C) to pregnant mice on GD9 impaired attentional set-shifting in offspring but surprisingly enhanced reversal learning. The deficit in set-shifting seemed to be mediated by the inhibition of PVIs in the mPFC, as suggested by the optogenetic activation/inactivation experiment (Canetta et al., 2016). In other studies, offspring of rats

that received poly(I:C) on GD 15 were impaired in reversal learning and had a higher number of non-perseverative errors in the ED part of the set-shifting digging task (Wallace et al., 2014). Rats in the poly(I:C) group also performed worse in a touchscreen reversal learning task but were surprisingly better in an operant lever pressing reversal task (Lins et al., 2018). However, in a study by Vorhees and colleagues, poly(I:C) rats had no deficit in reversal learning in the MWM (Vorhees et al., 2015).

Also, a MAM model produced deficits in set-shifting and reversal learning (Gastambide et al., 2012; Gomes et al., 2015; Moore et al., 2006). Similarly, in models based on maternal separation or social isolation was found an impairment of cognitive flexibility. Maternal separation for 3 hours a day during PD1-21 caused disruption of reversal learning in rats in the MWM (Xue et al., 2013) and the Barnes Maze (Filarowska-Jurko et al., 2022). McLean and colleagues (2010) found that rats socially isolated from weaning (PD 28) were impaired in ED shifting, and Powell et al. (2015) described deficits in reversal learning in socially isolated rats (form PD 24). On the other hand, in a study by Wang and colleagues (2015), the group that underwent repeated maternal separation (PD 1-21) had shorter escape latency in the MWM reversal stage.

Two-hit and three-hit models showed ambiguous results, as the second hit exacerbated the deficit in some studies, while in others, it seemingly protected against the next adversity. For example, mice prenatally exposed to poly(I:C) were not impaired in a touchscreen reversal task, and female mice were even better compared to their counterparts in the control group. However, the poly(I:C) group that was socially isolated after being previously housed in an enriched environment had worse performance (Zhao et al., 2021). In a study by Gomes et al. (2015), deficits caused by prenatal MAM exposure were not further exacerbated by cannabinoids in adolescence, and exposure to cannabinoids even ameliorated amphetamine-related hyperlocomotion. Also, in a study on mice that combined prenatal poly(I:C) exposure and social isolation, authors found that some alterations appeared after poly(I:C) or social isolation alone (e.g., hyperlocomotion, deficits in reversal learning and associative memory, but also changes in mTOR activation, higher cytokine levels and so on), but in a group that underwent both of the insults, almost all of them vanished. The results suggest that one adversity may build resilience against consequent negative life events (Goh et al. 2020). On the other hand, in one recent study, authors combined three factors: 1) a genetic manipulation (a partial deletion of microtubule-associated protein 6 MAP-6), 2) early life stress, and 3) cannabinoid exposure during

adolescence, and showed that mice in the three-hit group were more severely impaired compared to mice in the two-hit group (Bouet et al., 2021).

Optogenetic and chemogenetic models

The optogenetic and chemogenetic approach allows accurate activation or inactivation of the examined area or cell type. As such, it enables more precise manipulation of the studied area compared to pharmacological or developmental models. Furthermore, a within-subject design may be used. In line with previous studies, optogenetic activation of excitatory ventral hippocampal neurons in mice resulted in increased locomotion, sensitivity to amphetamine and impaired spatial novelty preference in the Y-maze without increasing anxiety in the EPM or changing place preference (Wolff et al., 2018). Similarly, optogenetic silencing of the ventral hippocampus in rats that previously underwent repeated administration of PCP alleviated the impairment in an eye-blink conditioning task caused by PCP (Fan et al., 2019). Furthermore, optogenetic activation of PVIs directly increased gamma oscillations (Cardin et al., 2009; McNally et al., 2021) that were repeatedly described to be altered in schizophrenia and caused hyperlocomotion and impaired novel object recognition (McNally et al., 2021). Furthermore, a recent study on rats from our lab by Patrono et al. (2023) showed that optogenetic stimulation of PVIs in the PFC and ventral hippocampus alleviated the deficit in the set-shifting digging task caused by acute administration of MK-801, supporting the link between the PVIs, gamma oscillations, and cognitive flexibility deficits.

1.5.2 Rodent models relevant to obsessive-compulsive disorder

Obsessive-compulsive disorder (OCD) is a chronic psychiatric disorder with a lifelong prevalence of 2-3% (Ruscio et al., 2010). It is characterized by the presence of obsessions and/or compulsions, which are time-consuming and severely disrupt the life of the affected person. Obsessions are repetitive, intrusive thoughts, images, or urges that typically increase anxiety. Compulsions are ritualistic physical or mental acts that the person performs to neutralize the anxiety caused by obsessions (APA, 2013). OCD is a heterogeneous disorder with several symptom subtypes, the most frequent being contamination obsessions accompanied by cleaning compulsions and fear of harm with checking compulsions (Ruscio et al., 2010).

OCD is a multifactorial disease, with genetic factors explaining approximately 40% of the variability and environmental factors around 50% (Taylor, 2011). The imbalance

between the direct and indirect pathways of cortico-striato-thalamo-cortical circuits (CSTC) has been suggested as a pathophysiological mechanism. Imbalance in the CSTC leads to increased activity of the direct pathway and subsequent disinhibition of the thalamus and hyperactivity of the prefrontal cortex, which is thought to promote repetitive behavior (Saxena & Rauch, 2000). Hyperactivity in the OFC, ACC and striatum has been repeatedly described in patients with OCD (Menzies et al., 2008), as well as alternations in the parietal and dorsolateral PFC (Li & Mody, 2016). These areas are implicated in several executive functions, such as planning, decision-making, error monitoring, inhibition, or working memory (Fitzgerald et al., 2011). Furthermore, changes in brain connectivity have been described in OCD patients. Especially resting state dysconnectivity between the striatum and cortical networks, hypoconectivity between the thalamus and striatum and dysconnectivity between the ACC and fronto-limbic regions. Interestingly, alterations in connectivity correlated with symptom severity and age of onset (Liu et al., 2022).

Also, disruption in neurotransmitter signalization has been suggested as a possible neuropathological mechanism, especially serotoninergic and glutamatergic. The serotonin hypothesis has been popular, given that selective serotonin reuptake inhibitors (SSRIs) are used as a first-line treatment for OCD. Furthermore, OCD has been associated with genes encoding catechol-o-methyl transferase (COMT), serotonin transporter, or serotonin 2A receptor (Meira-Lima et al., 2004). However, only around 40-86 % of patients respond to the established treatment, and the treatment response is often incomplete (Foa et al., 2005). Therefore, other possible treatment targets have been suggested, especially glutamatergic neurotransmission, which seems to be altered in patients with OCD. Higher concentrations of glutamate and glycine have been found in the cerebrospinal fluid (Bhattacharyya et al., 2009; Chakrabarty et al., 2005), OFC (Whiteside et al., 2006), ACC and caudate nucleus (Rosenberg et al., 2000) of OCD patients. Also, functional glutamatergic hyperactivity at rest has been found in OCD patients, especially in areas of the OFC, ACC, and caudate nucleus (Maia et al., 2008; Menzies et al., 2008), together with hypoactivity in the nucleus accumbens (Figee et al., 2011). Furthermore, adjacent therapy with drugs influencing glutamatergic neurotransmissions, such as riluzole, memantine, or amantadine, seems to improve OCD symptoms (Coric et al., 2005; Haghighi et al., 2013; Naderi et al., 2019).

Genetic models

Several transgenic and knockout mice that present repetitive behavior have been developed. For example, Sapap3[9] knockout mice or D1CT-7 mutant mice with a hyperactive direct pathway have been shown to express OCD-like behavior, such as excessive grooming, repetitive behavior, skin and hair biting and tic-like movements (Nordstrom & Burton, 2002; Welch et al., 2007). Interestingly, increased anxiety and compulsive grooming in Sapap3 mice were reduced after repeated administration of SSRI fluoxetine, supporting the predictive validity of the model (Welch et al., 2007). Another model relevant to OCD is Slitrk5 knockout. Slitrk5 is a gene encoding transmembrane proteins, and knockout mice manifest excessive grooming and increased anxiety, which can be alleviated by fluoxetine.

Furthermore, neurobiological abnormalities were described, such as hyperactivity in the OFC and alterations in the striatum and glutamate receptor composition (Shmelkov et al., 2010). Also, 5-HT2c knockout mice and mice with knockdown of presynaptic dopamine transporter show OCD-related behavior. 5-HT2c receptor knockout mice presented more chewing of non-nutritive clay and reduced habituation of head dipping (Chou-Green et al., 2003), while DAT knockdown mice showed stereotypical behavior patterns, hyperactivity and increased novel object exploratory activity (Berridge et al., 2005; Zhuang et al., 2001). However, 5-HT2c knockout mice performed better in an operant reversal task (Nilsson et al., 2012). In one study with Sapap3 mice knockouts, authors found impaired reversal learning in a conditioning visual reversal task (van den Boom et al., 2019). However, Benzina et al. (2021) did a translational study on OCD patients and Sapap3 KO mice and found no effect of group on reversal performance in either humans or mice when taken as a whole, but when separated by the OCD subtype dimensions, they found reversal learning impairment in part of patients with checking compulsions. In mice, cluster analysis revealed a subgroup of Sapap3 KO mice that were impaired in a reversal task. Similar results were described in a previous study, where Sapap3 KO mice had heterogeneous performance in reversal task, with approximately half having normal and half impaired performance (Manning et al., 2019). Interestingly, in neither of the studies, the performance in reversal task correlated with compulsive behavior (grooming).

[9] Sapap3 is a part of postsynaptic density components that together with other proteins form scaffolding complex at excitatory glutamatergic synapses. Sapap3 is the only one expressed in the striatum (Welch et al., 2007).

Pharmacological models

One of the established animal models is based on the chronic administration of D2/D3 receptor agonist quinpirole, which was used primarily to study compulsive checking. Quinpirole was found to produce hyperlocomotion and specific „checking" of objects in the open field. This behavior in rats was attenuated by antidepressant medication (Szechtman et al., 1998, 1999) and deep-brain stimulation of the orbitofrontal cortex (Flores-Vargas et al., 2019). Interestingly, lesions of the NAc core in rats increased checking, suggesting that the effect of quinpirole might be mediated by the inhibition of NAc neurons (Dvorkin et al., 2010). Also, a study from our lab on the rat quinpirole model reported stereotypical revisiting of objects and places in the open field and linked it with decreased plasticity-related activity in the CA1 of the hippocampus (Brozka et al., 2021). Another study showed deficits in a reversal in the AAPA task after acute administration of quinpirole to a previously sensitized group (Hatalova et al., 2014). This is in line with a previous study reporting impaired performance in an operant spatial reversal task in rats after quinpirole administration (Boulougouris et al., 2009). Also, intra NAc microinfusions of D1 receptor antagonist (SCH23390) and D2 receptor agonist (quinpirole) impaired set-shifting in a visual operant task, with SCH23390 increasing regressive errors, suggesting an impaired ability to maintain novel strategy and quinpirole increasing perseverative errors (Haluk & Floresco, 2009). Also, later studies indicated the importance of NAc core D2 medium spiny neurons for reversal learning and set-shifting. However, blocking them with D2 receptor agonists was associated with faster incorrect responses toward outdated reward cues. Similar results were found in NAc D2 knockout mice (Macpherson et al., 2016, 2022). Other OCD-relevant models are based on the acute administration of 5-HT1B/1A receptor agonist RU24969 and 1A agonist 8-hydroxy-2-(di-n-propylamino) tetralin (8-OH-DPAT). RU24969 has induced several OCD-like behaviors, such as PPI deficits, hyperactivity, perseveration, and route stereotypy in the open field. Importantly, deficits were attenuated by chronic treatment with fluoxetine or clomipramine (Ho et al., 2016; Shanahan et al., 2011). 8-OH-DPAT produced hyperlocomotion and checking-like behavior similar to quinpirole (Alkhatib et al., 2013).

Neurodevelopmental and spontaneous models

One of the neurodevelopmental models relevant to OCD is the neonatal clomipramine model, based on the premise that neonatal administration of the drug may have opposite effects to those found after administration in adulthood (Andersen, 2005). Paradoxically, tricyclic antidepressant clomipramine has been successfully used to treat

OCD, but neonatal administration induces several behavioral deficits. In one study, repeated administration of clomipramine to rat pups (PD 9-16) twice daily induced anxiety, perseveration in the spontaneous alternation task, impairment in reversal learning and working memory and corticostriatal dysfunction (elevated D2 receptors in the striatum and serotonin 2C receptors in the OFC) in adulthood (Andersen et al., 2010).

In spontaneous models, mice or rats are split into high-stereotypy and low-stereotypy subgroups. For example, spontaneous stereotypy (e.g., jumping, running in patterns) has been repeatedly described in deer mice reared in laboratory conditions, and the stereotypy was alleviated with fluoxetine (Korff et al., 2008; Powell et al., 1999). The stereotypy was also prevented in deer mice by raising them in an enriched environment. Interestingly, the stereotypy score was significantly correlated with the number of errors in reversal learning in the T-maze (Tanimura et al., 2008). Inflexible behavior has been further described in tasks like reinforced spatial alternation or marble burying. Tsaltas and colleagues showed that a subset of rats continued to select one arm in reinforced spatial alternation in the T-maze, and this nonflexible preference for one arm was enhanced by nonselective serotonin agonist mCPP and suppressed by chronic pretreatment with fluoxetine (Tsaltas et al., 2005). Another related paradigm is the signal attenuation model, based on the hypothesis that compulsive behavior may result from deficient feedback (Joel, 2006). The paradigm was developed in an operant conditioning task, where rats were trained in several steps. They first learned to collect the food pellets from a food container and then to associate compound stimulus (ligh+sound) with the food delivery. Later, the levers were installed, and they learned to induce the stimulus by lever pressing. In the stimulus attenuation phase, levers were absent, and the compound stimulus did not lead to food delivery. The stimulus attenuation led to compulsive lever-pressing in the test phase when rats compulsively pressed the reinforced lever without searching for food in the food container (Joel & Avisar, 2001). This behavior was again alleviated by acute pretreatment with antidepressants (Joel & Avisar, 2001).

Optogenetic, chemogenetic and lesion models

One study looked at the role of the orbitofrontal cortex and ventromedial striatum in OCD-like behavior in mice and found that repeated optogenetic hyperactivation of the OFC-VMS, leads to an increase in persistent grooming behavior, but in no other behavior measures, like PPI and anxiety (Ahmari et al., 2013). However, a similar study on rats failed to replicate the results. Optogenetic OFC-VMS stimulation, in this case, didn't increase grooming or affect set-shifting, marble burying and nestlet shredding, despite physiological

changes detected by electrophysiology and immediate early gene expression (de Oliveira et al., 2021). In another study, optogenetic stimulation of the lateral OFC and its terminals in the striatum in *Sapap3* knockout mice suppressed compulsive grooming (Burguière et al., 2013). A different study used optogenetic, chemogenetic and lesion approaches to dissect neural circuits responsible for goal-directed and habitual action implicated in OCD. Lesions to the dorsomedial striatum and OFC, as well as chemogenetic inactivation of the OFC (by hM4Di DREADD and CNO injection), resulted in habitual responding in an operant task, while optogenetic activation of the lateral OFC increased goal-directed behavior and enhanced a shift from habitual back to goal-directed action (Gremel & Costa, 2013). It is in line with a study by Burguière et al. (2013), in which stimulation of the lateral OFC decreased compulsive behavior. The OFC is also important for cognitive flexibility, as shown in a study by Boulougouris and colleagues, where lesions of the OFC selectively impaired reversal learning in an operant task in rats by increasing perseverative responses without impairing learning of new information per se (Boulougouris et al., 2007).

1.5.3 Rodent models relevant to autism spectrum disorder

Autism spectrum disorder (ASD) is a set of neurodevelopmental disorders characterized by three main symptom clusters: decreased reciprocal social interaction, impaired communication, and repetitive, restricted behavior, interests, or activities. Children and adults with autism may experience difficulties in emotional intelligence, social awareness, appropriate social responses, verbal and nonverbal communication, and the ability to form and sustain peer relationships. They may further have a higher sensitivity to sensory stimuli, excessive adherence to rules and lack of adaptability to new circumstances. Intellectual functioning, language abilities, as well as the ability to function in daily life widely vary among individuals along the spectrum (WHO, 2019). ASD develops on a heterogenous background involving genetic and non-genetic factors and their interaction and usually manifests in the first three years of life. Although twin studies point towards high heritability (between 64% and 91%) with ASD concordance rates of around 95% in monozygotic twins and under 5% in dizygotic twins (Nordenbæk et al., 2014; Taniai et al., 2008; Tickett al., 2016), it is also influenced by environmental factors. Environmental factors linked to ASD risk are mainly adversity during prenatal development, such as maternal infection (Jiang et al., 2016), maternal metabolic or autoimmune conditions (Krakowiak et al., 2012; Lyall et al., 2014), use of some kind of medication, such as valproic acid (Christensen et al., 2013), advanced maternal and paternal age (Idring et al., 2014), or

birth complications, including preterm birth or low birthweight (Lampi et al., 2012). Neurobiologically, ASD symptoms seem to be underlined by alterations in brain development. Toddlers with ASD have significantly increased brain volumes accompanied by larger head circumference, while in adolescence, the brain volume declines, so it doesn't differ from typically developing controls. However, the volume of many structures further atypically decreases in adulthood in ASD (Lange et al., 2015). Furthermore, disorganization of prefrontal and temporal cortical layers increased dendritic spine densities, altered myelination, and white matter fiber tract development, which consequently leads to dysfunctional connectivity, has been described in children with ASD (Galvez-Contreras et al., 2020; Hutsler & Zhang, 2010; Stoner et al., 2014; Wolff et al., 2012).

Genetic models

Although ASD is a genetically heterogenous disorder, several syndromes induced by a single gene mutation are linked with a higher risk for ASD, especially fragile X syndrome (mutation in FMR1), Phelan-McDermid syndrome (deletion of SHANK3 gene in the 22q13 region), Timothy syndrome (mutation in CACNA1C) and Prader-Willi syndrome (duplication of 15q11-14). Inherited de novo SHANK[10] mutations have been described in some patients with ASD (Leblond et al., 2012). Several animal models related to ASD were developed based on a single gene mutation found in human patients (although those account for a small subset of ASD cases (Genovese & Butler, 2020)), followed by many other genetic models that mainly target genes and proteins that have an essential role in brain development (Ergaz et al., 2016). Mentioned mice models have been found to express autism-related behavioral traits, especially impaired social behavior (measured in the three-chamber and the open field), decreased social communication (measured by ultrasonic vocalizations) and repetitive grooming, jumping and digging (Ey et al., 2013; Garrido et al., 2022; Mineur et al., 2006; Moon et al., 2018; Peça et al., 2011; Wang et al., 2017; Won et al., 2012). Some studies also report impaired (spatial) learning (Kouser et al., 2013), while others found no impairment (Peça et al., 2011; Yang et al., 2012).

Cognitive flexibility deficits have been described in various models relevant to autism. SHANK3 knockouts have been found to have impaired reversal learning in the MWM, but also spatial learning in general (Kouser et al., 2013) as well as impaired pairwise

[10] SHANK is a part of PSD95/SAPAP/SHANK postsynaptic complex, important for synaptic development and function (Naisbitt et al., 1999).

visual discrimination learning in a touchscreen task (Copping et al., 2017), suggesting wider cognitive impairment. On the other hand, in another study, they were slightly impaired only in the reversal probe trial in the MWM but not in previous phases of the task (Yang et al., 2012). Also, male but not female SHANK2 knockout mice exhibited a deficit in reversal learning in a conditioning task (Yun et al., 2022). Rats with a heterozygous deletion of CACNA1C were impaired in a touchscreen reversal learning task (Sykes et al., 2019). Also, in several other knockout mice was described impairment in reversal learning, for example, in mice with a knockout in neurexin 1 gene, which has also been associated with ASD (Hughes et al., 2022), in mice lacking GluK2 subunit of kainate receptors (Micheau et al., 2014) or in Dlgap2[11] KO mice (Jiang-Xie et al., 2014).

Neurodevelopmental and other nongenetic models

Apart from many genetic models, several other ASD-relevant models have been developed by manipulating environmental factors or focusing on innate behavioral variability. Phenotypic traits relevant to autism have been described in several inbred mice strains, such as BTBR, BALB/c, or C58 (Ergaz et al., 2016). BTBR mice show increased self-grooming, decreased reciprocal social interaction and social approach, impaired juvenile play (McFarlane et al., 2008) and produce an altered pattern of ultrasonic vocalization: fewer USVs in adulthood (Yang et al., 2013), but more, louder and harmonically distinct USVs in the postnatal period (Scattoni et al., 2008). They also have a higher frequency of compulsive marble burying (Amodeo et al., 2012) and perseverative behavior, such as impaired reversal learning in the MWM (Moy et al., 2007). Similarly, BALB/c mice show deficits in social interaction (Jacome et al., 2011; Sankoorikal et al., 2006) without severe repetitive behavior (Jacome et al., 2011). C58 inbred mice show increased repetitive behavior, namely jumping and backflipping (Muehlmann et al., 2012; Ryan et al., 2010), decreased social approach in three chamber and impaired transmission of food preference (Ryan et al., 2010).

Reduced cognitive flexibility was also described in several models. BTBR *T+tf/j* mice showed worse performance in the probabilistic reversal task (Alvarez et al., 2023; Amodeo et al., 2012; Athnaiel et al., 2022) as well as in conditioning reversal task that required the use of contextual cues (Rutz & Rothblat, 2012). Similarly, C58BL/6J mice were

[11] Dlgap2 encodes one of the main components of postsynaptic density (Rasmussen et al., 2017).

described to have reversal learning impairments in probabilistic settings, although non-probabilistic reversal learning was spared (Whitehouse et al., 2017).

Other models relevant to ASD include, for example, prenatal exposure to valproic acid. Rat offspring exposed to valproic acid on GD 12.5 showed reduced PPI, hyperactivity, a higher number of repetitive behaviors and impaired social behavior (Schneider & Przewłocki, 2005). Furthermore, rats treated with valproic acid on GD12 had impaired set-shifting, which was pronounced mainly in ID shifting in female rats (McKinnell et al., 2021). Similarly, mice treated postnatally with valproic acid (PD14) showed impairments in reversal learning in the Y-maze and in this case, male mice had significantly worse performance than any other group (Norton et al., 2020). Also, MIA has been used as a model relevant not only to schizophrenia but also to ASD, as they are hypothesized to share partially similar pathological disturbances (Barlati et al., 2016). For example, exposure to poly(I:C) in GD 12.5 caused impairments in mice offspring similar to those found in BTBR mice, namely increased USVs in pups, impaired social behavior and increased marble burying (Pendyala et al., 2017; Schwartzer et al., 2013). Impairments in social behavior after prenatal exposure to poly(I:C) were described in many MIA studies (e.g., Amodeo et al., 2019; Hsiao et al., 2012; Naviaux et al., 2013; Pendyala et al., 2017; Vuillermot et al., 2017). Also, in MIA models relevant to ASD, a decreased cognitive flexibility was described, such as in a study by Amodeo et al. (2019), where exposure to poly(I:C) in GD 12.5 impaired probabilistic reversal learning in the T-maze and decreased social approach in the three-chamber.

2 Aims of the thesis

To assess (spatial) cognitive flexibility in several rodent models relevant to schizophrenia, obsessive-compulsive disorder, and autism spectrum disorder, as well as other related behavioral characteristics, especially perseveration, spatial learning, and memory.

Cognitive inflexibility is one of the prominent symptoms of schizophrenia, autism spectrum disorder and obsessive-compulsive disorder. Animal models of psychiatric or neurodevelopmental disorders are an essential tool for studying pathophysiology and potential treatment targets, however, their validity must be carefully assessed. Examining cognitive flexibility in rodent models together with other behavioral manifestations helps to characterize the model and adds up to the face validity. Therefore, we first aimed to replicate previously established models of schizophrenia and OCD and to further study the spatial cognitive flexibility and related aspects in these models. In CRMP2 knockout mice - a novel model relevant to ASD - we aimed to characterize the model to examine its validity.

To assess cognitive deficits and the role of parvalbumin interneurons in a two-hit mice model relevant to schizophrenia.

Maternal immune activation is an established model relevant to schizophrenia and other neurodevelopmental disorders, such as autism spectrum disorder. In schizophrenia patients, set-shifting deficits are among the most consistent findings (e.g., Ceaser et al., 2008; Jazbec et al., 2007; Pantelis et al., 1999). Attentional set-shifting relies on correct hippocampal-prefrontal communication (Floresco et al., 2009), which seems to be underlined by GABAergic parvalbumin-positive interneurons (Cho et al., 2015). Therefore, our study examined attentional-set shifting and other behavioral characteristics in the mice two-hit model relevant to schizophrenia. The mice offspring underwent prenatal immune challenge with poly(I:C) on GD9 and chronic, unpredictable stress in periadolescence (as described in Giovanoli et al., 2013). They were behaviorally tested in adulthood. Furthermore, changes to PVIs were assessed.

To assess the role of antiglutamatergic agents on spatial learning and cognitive flexibility in two pharmacological rat models relevant to OCD.

Although serotonin is the main neurotransmitter implicated in the pathophysiology logy of OCD, disruption in other systems, especially glutamatergic, has also been implicated. Therefore, we aimed to study the effects of memantine and riluzole (drugs decreasing

glutamatergic neurotransmission) in two established rat models relevant to obsessive-compulsive disorder. Firstly, we attempted to induce the quinpirole and 8-OH-DPAT pharmacological models and examine sensitized and control rats' spatial learning and cognitive flexibility in the Active Allothetic Place Avoidance task (AAPA). Furthermore, we examined if pretreatment with memantine and riluzole will prevent the possible deficits caused by the sensitization to quinpirole and 8-OH-DPAT and enhance the AAPA performance.

To assess a behavioral phenotype of CRNP2 knockout mice.

Disruption in proteins involved in neurodevelopmental processes is implicated in disorders, such as autism spectrum disorder or schizophrenia. To examine the role of collapsin response mediator protein 2 (CRMP2) in neurodevelopmental processes, newly generated CRMP2 full knockout mice (*crmp2-/-*) were developed. Several behavioral tests were conducted to assess the relevance of the CRMP2 KO mice model to neurodevelopmental disorders, especially ASD. Ultrasonic vocalization was measured in juvenile age (PD 6-12), and tests focusing on sociability, cognitive flexibility, perseveration and memory were assessed in adulthood.

3 Methods

This thesis is based on four original articles inserted in the appendix, where the methods are described in further detail. Here I briefly describe the most important methods used in the studies.

3.1 Induction of the models

3.1.1 Two-hit model of schizophrenia based on the prenatal poly(I:C) application and mild chronic stress in periadolescence

We applied the poly(I:C) (potassium salt, Tocris) at a dose of 5 mg/kg to pregnant C57BL/6N (Charles River) mice (N = 16) on gestational day 9, which should correspond to the first or early second trimester in humans (Workman et al., 2013). Mice offspring further underwent unpredictable stress in periadolescence that was previously found to boost an impairment caused by MIA (Giovanoli et al., 2013, 2014, 2016). Offspring were kept in the IVC system until adulthood (approximately 60 days of age) and transferred to standard open cages (26 × 20.5 × 13.5 cm) one week before the start of behavioral testing. Half of the pups (n = 19) underwent mild chronic stress every other day between PD 30 and 40. Five different stressors were used: three mild shocks (0.3 mA, PD 30), restraint stress for 45 min (PD 32), water deprivation for 16 h (PD 34), two one-minute long forced swimming sessions (PD36), and repeated changes of home cages during the dark phase of the light/ dark cycle (PD38). Mice in the control group (n = 17), which did not undergo the stress protocol, were taken out of the cage and briefly handled (15 s) by the same experimenter. Both male (n = 15) and female (n = 21) offspring were used for behavioral experiments and quantification of PVIs in the hippocampus.

3.1.2 Pharmacological models of OCD based on quinpirole and 8-OH-DPAT sensitization

The Long-Evans rats were injected subcutaneously with D2/D3 receptor agonist quinpirole (0.25mg/kg), serotonin 1A/7 agonist 8-OH-DPAT (0.25 mg/kg) or saline (1 ml/kg) every other day (10 injections in total). Immediately after the injection, the rats were put into the rotating Carousel maze without the activated shock sector, so they could explore freely and habituate to the rotating arena for 50 min. In the acquisition phase, they were injected with memantine, riluzole (1mg/kg or 5mg/kg in the quinpirole study and 1mg/kg in

the 8-OH-DPAT study) or saline 30 minutes before the session and with quinpirole, 8-OH-DPAT or saline right before the experimental session. Fifty-six rats were tested in the quinpirole study and ninety-eight rats in the 8-OH-DPAT study.

3.1.3 CRMP2 knockout model

Crmp2-/- mice were developed in the Laboratory of Molecular Neurobiology, as described in Žiak et al., 2020.

3.2 Behavioral methods

Spatial set-shifting task

Set-shifting was tested in a non-transparent, white cross maze, where a removable wall blocked one of the arms. The task was based on switching between egocentric and allocentric navigation, as described in Torres-Berrío et al. (2019). The whole procedure consisted of one habituation session and ten experimental sessions: five sessions of learning in the egocentric condition and five sessions of the allocentric condition (with a switch on day 6). Colorful geometrical shapes attached above each arm were used as visual cues. The results were calculated as the % of incorrect trials from each session for both parts. For the second part, we specifically calculated never-reinforced (old information) and perseverative (new information) errors.

Locomotion and sensitivity to amphetamine in the open field

Locomotion and sensitivity to amphetamine were tested in an open field (50 × 50 cm) in two sessions. On the first day, mice were injected with saline solution and placed into the maze for 30 minutes to assess locomotion. The next day, they were injected with amphetamine (D-amphetamine sulfate, Sigma-Aldrich; 2.5 mg/kg, subcutaneously) immediately before the 90-minute session in the open field. Both sessions were recorded and analyzed with the Ethovision system (Noldus, Wageningen, The Netherlands).

Anxiety in the Elevated Plus Maze

Anxiety was assessed in the Elevated Plus Maze (EPM), which is a plus-shaped maze with two opposite arms enclosed with walls, two open arms, and a central area. The mice were placed at the central part of the maze facing one of the open arms, and their behavior was recorded for five minutes. Videos were analyzed manually in BORIS software.

Prepulse inhibition

Prepulse inhibition of the startle reflex (PPI) is used in both humans and animals to measure sensorimotor gating and early information processing. We tested the animals in an

acoustic startle response chamber (Coulbourn Habitest, Pennsylvania, USA) and calculated the PPI as the percent difference between prepulse-pulse and pulse-alone trials according to the formula (startle response to pulse alone - startle response to prepulse-pulse)/startle response to pulse alone) x 100.

The Active Allothetic Place Avoidance task (AAPA)

The AAPA was used to study spatial memory and cognitive flexibility. The apparatus (carousel maze) consists of an elevated metallic disc surrounded by a transparent plastic wall. It rotates clockwise at one rotation per minute, and the visually imperceptible 60° to-be-avoided sector is defined inside the arena, where rodents receive mild foot shocks until they leave the sector. The rodents must learn to coordinate arena and room frames and use only extra-maze cues (e.g., posters on the wall) to navigate the maze and avoid the to-be-avoided sector. The intensity of foot shocks is adjusted individually (0.2–0.6 mA) and kept to the minimum possible level to elicit an escape response and motivate the animal to learn the sector position.

Ultrasonic vocalization

Ultrasonic vocalizations emitted by socially isolated pups were recorded on postnatal days (PD) 6, 8, and 12. Each pup was taken from its home cage and recorded for 5 minutes in a Styrofoam box with a microphone (Dodotronic Ultramic 250K, Italy) and Audacity software. The vocalizations were analyzed with Avisoft-SASLab Pro.

Social approach and social novelty in the Three-chamber task

Three-chamber task was used to assess sociability and social novelty preference. The apparatus (54 x 20 x 33 cm) was made from clear plexiglass, and the chambers were divided by transparent walls with squared openings (5 x 5 cm) and sliding doors. Each mouse was first placed in the middle compartment for 10-minute habituation. An unknown male mouse (stranger 1) was then enclosed in a little wire cage and placed in either the left or right compartment, and a black plug (4.5 cm in diameter) was used as an object and placed in the opposite compartment inside an identical wire cage. The position of the stranger mouse and object was counterbalanced between trials, and stranger mice were previously habituated to the cage. The sliding doors were then opened, and the test mouse could explore the apparatus for 10 minutes freely. After this part of the experiment, another unknown mouse (stranger 2) was put inside the same chamber instead of the object. The test mouse was then allowed to explore all chambers for another 5 min. The behavior was recorded by a camera placed above the apparatus. Time spent in each chamber and time spent sniffing the wire cages were analyzed manually in BORIS software.

Working memory and perseveration in the Y-maze

We tested the spontaneous alternation in the Y-maze (with 35 cm long, 6 cm wide, and 18 cm high arms). Arms were marked as A, B, C, and mice were put into the A-arm and let to freely explore the apparatus for 8 minutes. Spontaneous alternation was measured as the ratio of actual triads (sequence of arms visits) to potential triads (perfect alternation performance).

3.3 Immunological assays

Verification of immune response

We measured IL-6 levels in non-pregnant female mice (n = 3-4 per treatment group) three hours after the application of poly(I:C) (5 mg/kg) or saline. Mice were anesthetized with isoflurane, and blood was collected by cardiac puncture into an anticoagulant-containing tube. Samples were centrifuged at 2500 g, 4 ◦C for 10 min, and separated plasma was used for further analysis with mouse IL-6 ELISA kit (Sigma-Aldrich, RAB0308).

Immunohistochemistry on parvalbumin-positive interneurons

Immunohistochemistry and brain preparations were done as described earlier in Brozka et al. (2017). We used a rabbit PV antibody (1:1000, Abcam, ab11427) as the primary antibody and an Alexa Fluor Plus 555 (1:1000, Invitrogen, A32732) as a secondary antibody. PVIs in the CA1, CA2, CA3, and dentate gyrus of the hippocampus were counted, and the size of the areas was measured on a BX53 microscope (Olympus, Japan). Analyzed sections ranged from -1.36 to -2.36 relative to *bregma.*

4 Results

Here I briefly describe the most important results related to the topic of this thesis. Further details can be found in the original papers in the appendix.

4.1 Two-hit model of schizophrenia based on the prenatal poly(I:C) application and mild chronic stress in periadolescence

We found a selective deficit in the spatial version of set-shifting in the group exposed to poly(I:C) in the prenatal period, with no effect of stress on the set-shifting performance (see Figure 8). Although the poly(I:C) at the dose of 5mg/kg induced strong immune activation (see figure 9), we found no effect of poly(I:C) or stress on the performance in other behavioral tasks (PPI, amphetamine sensitivity, locomotion in the open field, and anxiety in the EPM). The analysis further showed a significant effect of stress on the number of parvalbumin-positive interneurons in the CA1 and CA3 regions of the hippocampus in females, but no effect of poly(I:C) (see Figure 10).

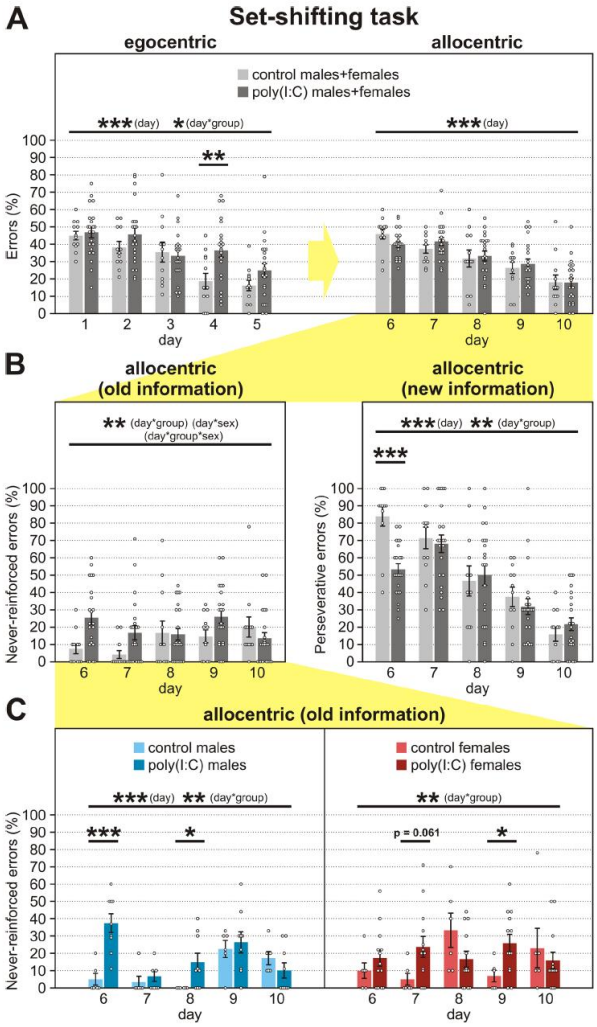

Figure 8. Results from attentional set-shifting. **A.** Mice in the poly(I:C) group had significantly more errors on the 4th day of the egocentric condition. **B.** Mice in the control group had significantly more perseverative errors on the 1st day of the allocentric condition (6th day of the experiment). **C.** Male mice in the poly(I:C) group had significantly more never-reinforced errors than the control group on the 1st and 3rd day of the allocentric condition (6th and 8th day of the experiment). Female mice in the poly(I:C) group had significantly more never-reinforced errors on the 4th day of the allocentric condition (9th day of the experiment). All data are presented as mean ± SEM, *p < 0.05; **p < 0.01; ***p < 0.001.

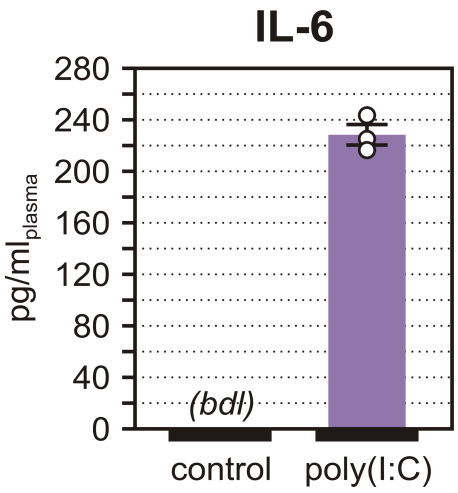

Figure 9. IL-6 levels after application of poly(I:C) or vehicle. Non-pregnant female mice (n = 3-4 animals per treatment group) were exposed to poly(I:C) or saline and plasma levels of pro-inflammatory cytokine IL-6 were measured three hours after the application using mouse IL-6 ELISA kit. High IL-6 plasma levels in the poly(I:C) treated group indicate that our batch of poly(I:C) at the dose of 5mg/kg induced strong immune activation.

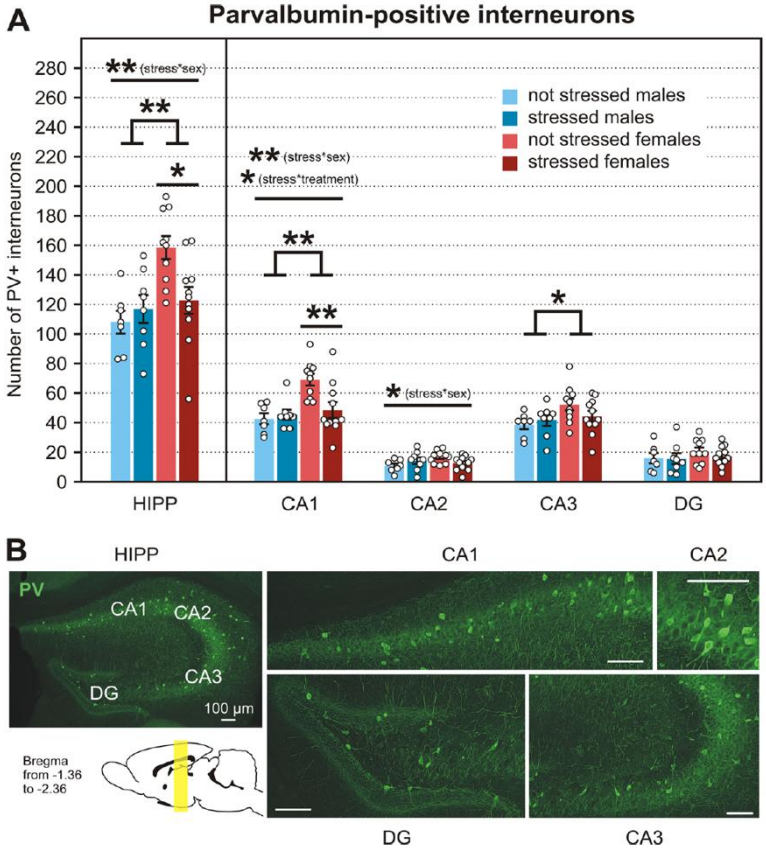

Figure 10. Parvalbumin-positive interneurons (PVIs) in the dorsal hippocampus of adult mice. **A.** Non-stressed female mice in the control group had the highest number of PVIs. Particularly, female mice had a significantly higher number of PVIs in the CA1 and CA3 regions compared to male mice. In the CA1 region, non-stressed female mice had significantly more PVIs compared to stressed female mice regardless of the treatment group.
B. Immunohistochemically stained PVIs in the hippocampus. Scale bars (for all images) = 100 µm. CA = *Cornu Ammonis*; DG = dentate gyrus; HIPP = hippocampus; PV = parvalbumin. All data are presented as mean ± SEM, *p < 0.05, **p < 0.01.

4.2 Pharmacological models of OCD based on quinpirole and 8-OH-DPAT sensitization

Sensitization with quinpirole and 8-OH-DPAT

We found that repeated treatment with quinpirole (0.25 mg/kg) and acute treatment with 8-OH-DPAT (0.25 mg/kg) produced significant hyperlocomotion in Long-Evans rats (see Figure 11). Furthermore, the treatment with both drugs impaired spatial learning in the

AAPA so severely that reversal couldn't be tested (see Figures 12-14). Importantly, the spatial impairment was not just a byproduct of hyperlocomotion, as the correlation between the number of entrances into the „shock" sector and locomotion in the quinpirole study was significant only for a quinpirole group pretreated with riluzole (1mg/kg). Similarly, the animals acutely treated with 8-OH-DPAT had more entrances to the „shock" sector per unit of distance.

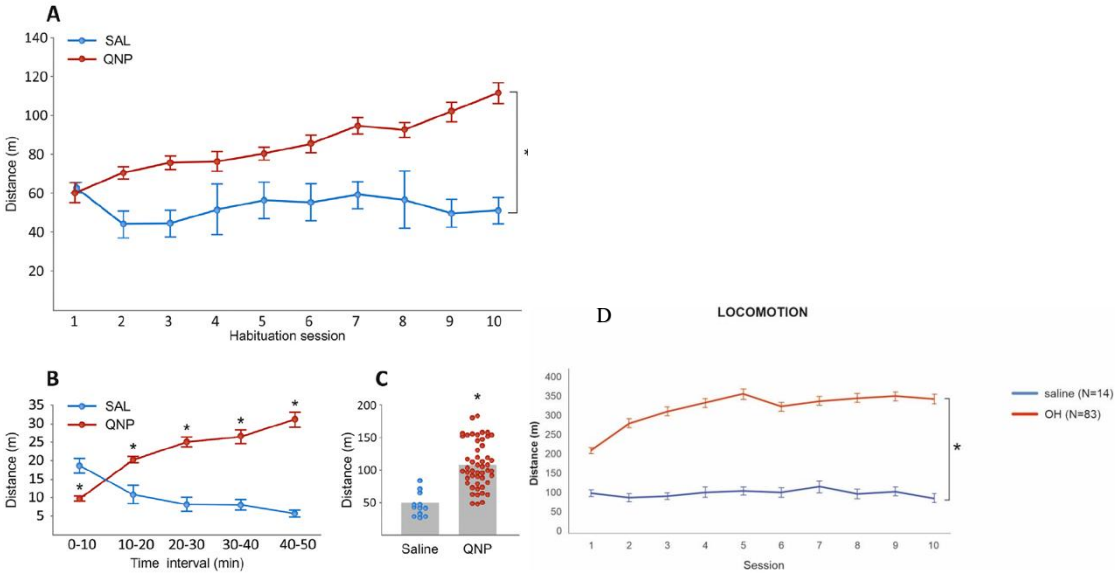

Figure 11. A. Locomotion of the quinpirole and saline groups during habituation (meters/50 min). On the last day of habituation, there was a significant increase of locomotion in the QNP group (QNP = 112 ± 33m, SAL = 53 ± 19 m). **B.** Mean changes in the locomotion of QNP and saline groups during the 10th session. Differences between both groups were significant in each time interval ($p \leq 0.001$). **C.** Significant difference between the QNP and saline group locomotion on the 10th day of habituation ($p < 0.001$). **D.** Locomotion in the 8-OH-DPAT group was significantly higher compared to control group from the first day of sensitization/habituation. * denotes a significant difference at $p = 0.01$. Data are presented as mean values ± SEM.

Effect of antiglutamatergic agents, memantine and riluzole

We further showed that neither memantine nor riluzole alleviated the deficit in spatial learning induced by quinpirole and 8-OH-PAT. Memantine at the dose of 5mg/kg significantly aggravated the deficit caused by quinpirole, and both memantine and riluzole (1mg/kg) exacerbated hyperlocomotion and learning deficit caused by 8-OH-DPAT. Importantly, memantine and riluzole had no detrimental effect on spatial learning or locomotion in saline groups, and a saline group treated with riluzole had slightly less entrantces to the to-be-avoided sector per unit of distance in the 8-OH-DPAT study. Therefore, the detrimental effect was caused by the interaction of memantine and riluzole with the quinpirole or 8-OH-DPAT (see Figures 12-14).

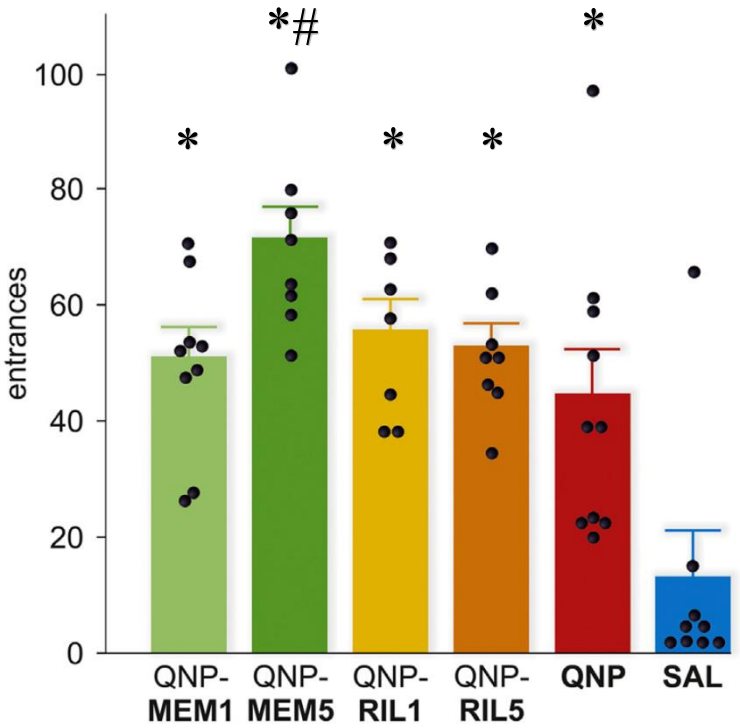

Figure 12. Entrances into the to-be-avoided sector of all treatment groups. All groups made significantly more errors than the control group ($p < 0.01$). The group treated with memantine 5 mg/kg made the highest number of errors, even significantly more than the quinpirole-saline group ($p < 0.05$). * denotes a significant difference from the saline control group at $p < 0.01$. # denotes a significant difference from the QNP-saline group at $p < 0.05$. Data are presented as an average number of errors ± SEM.

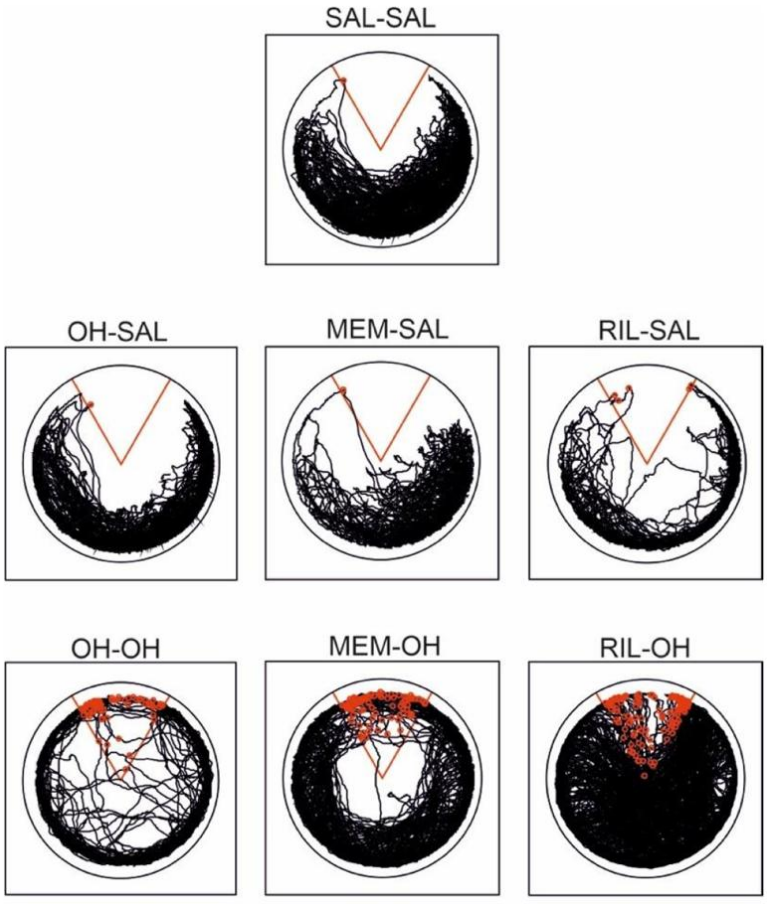

Figure 13. Typical trajectories of treatment groups on the 10th day of acquisition in the 8-OH-DPAT study. The SAL-SAL (control group) and OH-SAL groups avoided the sector well, as well as the MEM-SAL and RIL-SAL groups. All groups that received 8-OH-DPAT during acquisition had increased locomotion and did not avoid the shock sector efficiently. The RIL-OH group had the highest number of entrances to the to-be-avoided sector.

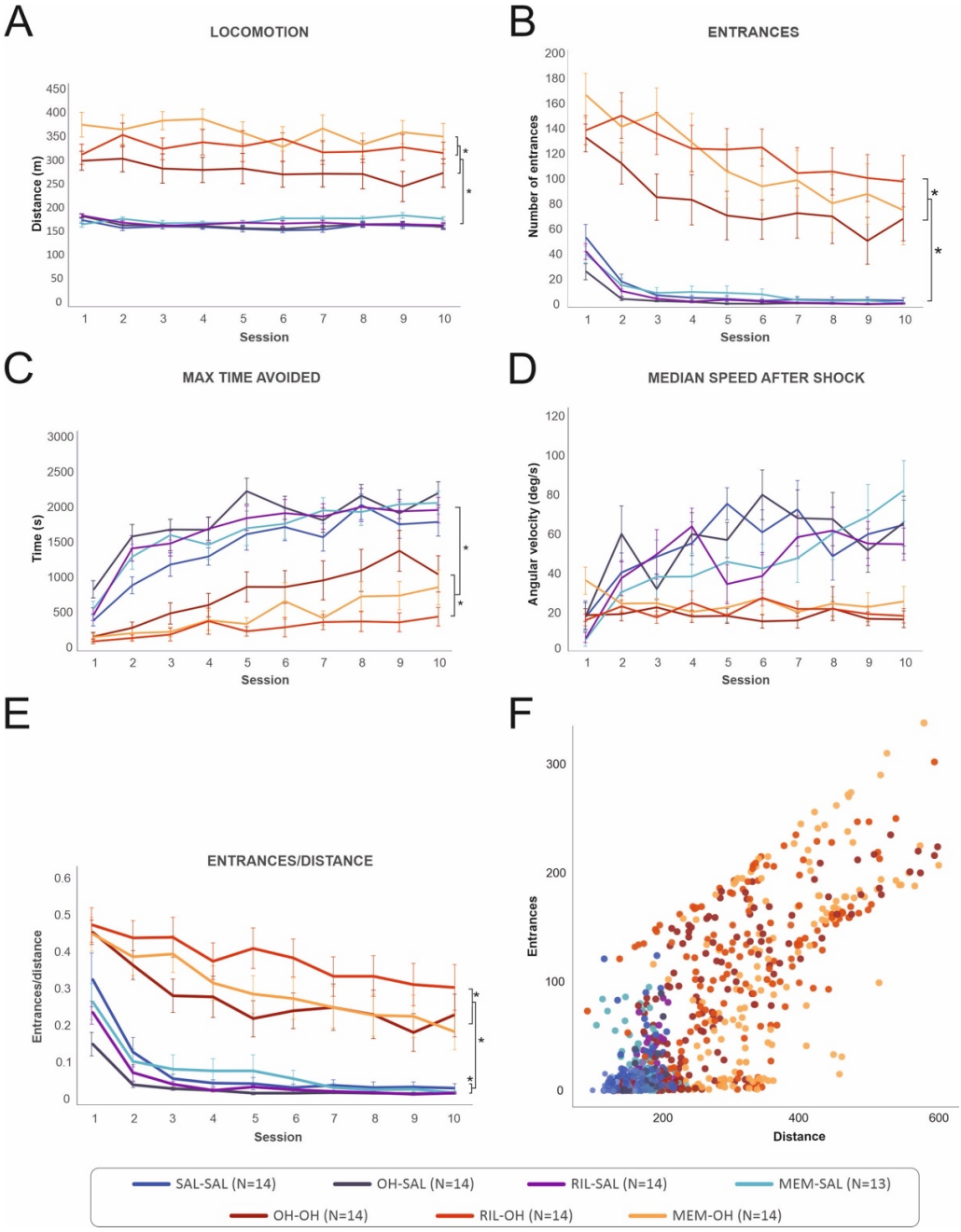

Figure 14. The behavior of all treatment groups during the 10 acquisition sessions in the five measured parameters. **A.** Locomotion was stable during all 10 sessions for each group, although it was significantly higher in the 8-OH-DPAT group compared to the "saline" groups. The MEM-OH and RIL-OH groups had significantly higher locomotion than the OH-OH groups. **B.** The number of entrances to the shock sector decreased across sessions, but it was significantly higher in the groups treated with 8-OH-DPAT during acquisition compared to the "saline" groups during all 10 sessions. The RIL-OH and MEM-OH groups had the highest number of entrances to the shock sector. **C.** Maximum time avoided was significantly longer in the "saline" groups than in the "OH" groups. **D.** Median speed after shock did not change in the "OH" groups and only slightly increased in the "saline" groups, but with noticeable variation across sessions. **E.** The entrances/distance parameter showed that the groups treated with 8-OH-DPAT during acquisition had a higher number of entrances compared to the "saline" groups, and the RIL-OH group had the highest number of entrances even when controlled for locomotion. The OH-SAL and RIL-SAL groups had the lowest number of entrances per distance. **F.** Correlation of locomotion and number of entrances. A higher number of entrances correlated with hyperlocomotion in some animals from the "OH" groups. * denotes a significant difference at $p = 0.05$. Data are presented as mean values ± SEM with the exception of Figure 3F, which presents each trial for each animal.

4.3 CRMP2 knockout mice

We showed that CRMP2 knockout mice had defects in axonal guidance, pruning, and dendritic spine remodeling. Furthermore, we found decreased social interaction (fewer USV calls) in pups, which is in line with impaired social interaction in ASD early in life. Importantly, reduced sociability endured into adulthood, as adult CRMP2 knockouts showed no preference for a social partner in the three-chamber test (see Figures 16 A-E). Surprisingly, CRMP2 knockouts had normal performance in the AAPA reversal task, although they had reduced spontaneous alternation in the Y-maze (see Figures 15 and 16 I). Furthermore, spatial learning and long-term memory were preserved, suggesting no severe cognitive deficit (see Figure 15).

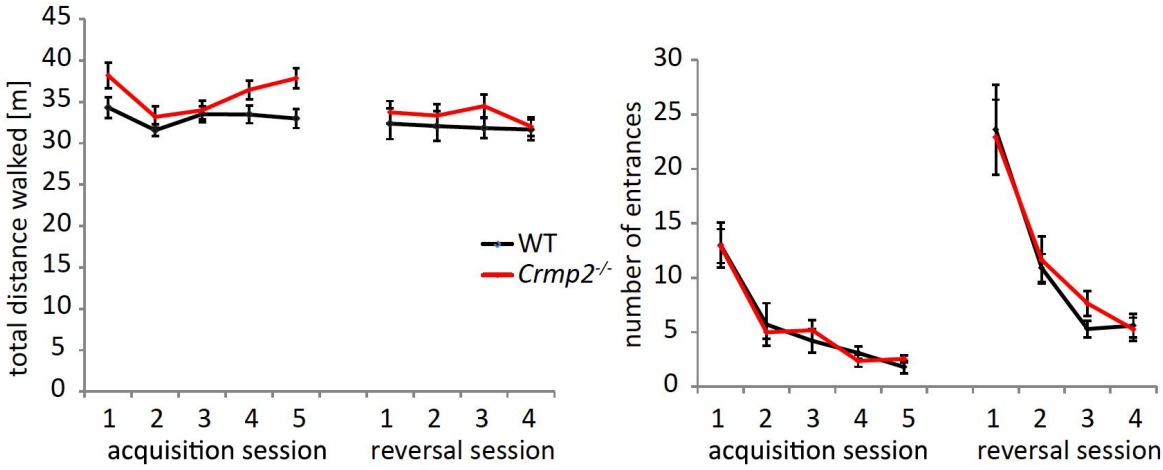

Figure 15. Results from the AAPA task. No significant difference was measured between WT and *crmp2-/-* mice in either acquisition or reversal, suggesting preserved spatial learning, memory, and cognitive flexibility. Data are presented as mean ± SEM.

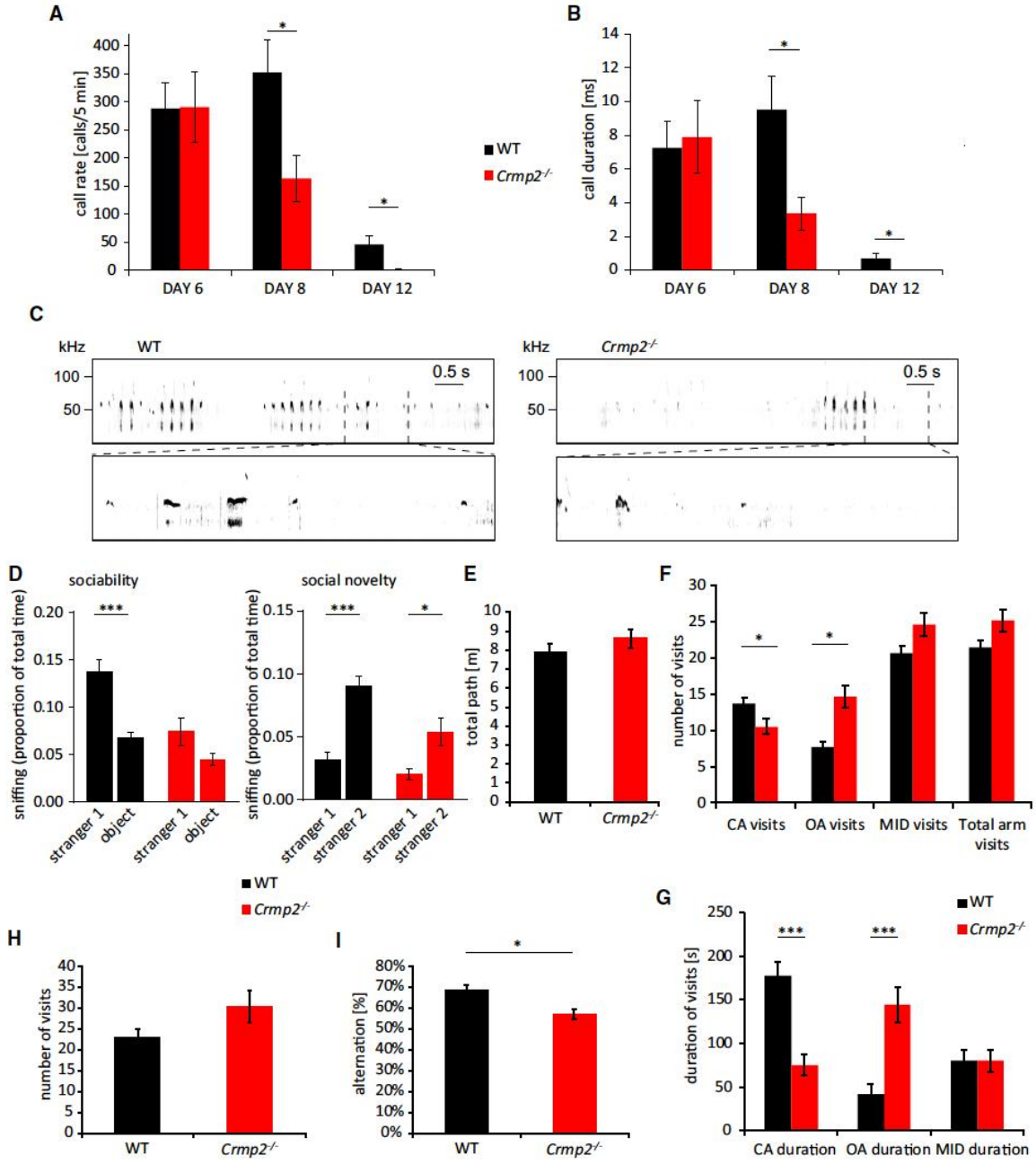

Figure 16. A, B. Ultrasonic vocalizations measured at PD6, PD8, and PD12 (WT = 14 pups, *crmp2-/-* = 13 pups). In *crmp2-/-* mice, there was a significant decrease in the rate and duration of calls at P8 and P12. Mean ± SEM, *p < 0.05. **C** Representative sonograms of the PD8 mice. **D** Three-chamber test (WT n = 11, *crmp2-/-* = 13). In the sociability phase, WT mice spent significantly more time with a social partner (p = 0.0001), while the difference was not significant in *crmp2-/-* mice (p = 0.07). In the social novelty phase, when an object was substituted with a second social partner (stranger 2), both WTs and knockouts preferred novel mice to known mice. Mean ± SEM, *p < 0.05, ***p < 0.001. **E–G** Elevated plus maze test (n = 10 mice/genotype). **E.** Total distance walked is similar in WT and *crmp2-/-(*p = 0.3). **F, G**. Frequency and duration of the open arms (OA) visits are increased in *crmp2-/-* mice suggesting decreased anxiety. CA denotes closed arms, MID denotes the transition zone between arms, and total arm visits represent a sum of visits in all four arms, mean ± SEM, *p < 0.05, ***p < 0.00. **H, I.** Y-maze (WT n = 9 mice, *crmp2-/-* n = 8 mice). Decreased alternations between arms of the Y-maze indicate impaired working memory or possibly increased perseveration. Mean ± SEM, *p < 0.05.

5 General Discussion

Studies focused on the neuropsychology of schizophrenia, obsessive-compulsive disorder (OCD) and autism spectrum disorder (ASD) often report impairments or alterations in the cognitive domain, including decreased cognitive flexibility. Cognitive rigidity has been implicated to enhance and maintain psychiatric symptoms, and many psychotherapeutic interventions focus on developing more flexible thought processes and behavior. In this thesis and inserted manuscripts, we examined the executive cognitive flexibility in spatial tasks in animal models relevant to schizophrenia, OCD, and ASD, as well as other behavioral and neurobiological characteristics.

Prenatal immune activation with poly(I:C) and chronic stress may induce selective deficit in spatial set-shifting and decreased number of parvalbumin-positive interneurons in the hippocampus.

Maternal immune activation with poly(I:C) has been shown to produce a broad spectrum of deficits in offspring. Epidemiological studies point to an increased risk of exposure to infection in early to mid-gestation. In particular, maternal infection in the first trimester leads to a sevenfold increase in the risk of schizophrenia development in offspring (Brown et al., 2004). Therefore, in our study, we applied the poly(I:C) (5mg/kg) to pregnant mice on gestational day 9, which should correspond to the first or early second trimester in humans (Workman et al., 2013). Mice offspring further underwent unpredictable stress in periadolescence in line with the hypotheses that genetic susceptibility or developmental insult paired with other environmental factors or adversity later in life may set off the onset of the disease (reviewed, for example, by Davis et al., 2016).

In the present study, we found impairment in the poly(I:C) group in a spatial set-shifting task based on the switch between egocentric and allocentric navigation in the cross maze. Notably, mice that underwent poly(I:C) exposure had more never-reinforced errors after a switch to allocentric condition, with male mice being slightly more impaired than female mice. Interestingly, there was no difference in perseverative errors, except for the first day of the allocentric condition when the control mice had significantly more perseverative errors compared to the poly(I:C) group. It may suggest an overall slower learning pace of the poly(I:C) mice, as they also had more errors on the fourth day of the egocentric condition. We found no effect of stress on set-shifting performance. Surprisingly, no difference between groups was found in prepulse inhibition, anxiety, locomotion, or sensitivity to amphetamine. Our finding of selective impairment in cognitive flexibility contrasts with

previous works that described broader behavioral impairment. Mainly, a decreased prepulse inhibition was often found (e.g., Carreño et al., 2020; Giovanoli et al., 2013, 2016; Li et al., 2009; Meyer, Murray et al., 2008; Vuillermot et al., 2010) together with higher sensitivity to amphetamine (e.g., Borçoi et al., 2015; Meyer, Murray, et al., 2008; Meyer, Nyffeler, et al., 2008) and social behavior impairment (e.g., Labouesse et al., 2015; Richetto et al., 2017; Vuillermot et al., 2017). However, some studies also failed to find a difference between groups. For example, Deane et al. (2021) found no PPI impairment in the poly(I:C) induced MIA rat model, and in a study by Goh et al. (2020), PPI was not influenced by either poly(I:C) exposure, or social isolation in a dual-hit model.

Several factors might mediate the lack of significant differences between groups in these behavioral tasks. Firstly, some recent studies showed that contrary to two-hit (or multiple-hit) hypotheses, multiple adversities may increase resilience. For example, in one study, authors combined prenatal poly(I:C) exposure with social isolation in mice and found that while both factors induced some behavioral and neurobiological changes separately, they seemed to protect against each other when combined (Goh et al., 2020). Similarly, Gomes et al. (2015) showed that cannabinoids in adolescence did not further exacerbate deficits caused by prenatal MAM exposure, and the cannabinoids even ameliorated amphetamine-induced hyperlocomotion. The diverging results indicate a more complicated relationship between adversity, vulnerability, and resilience. Under different circumstances, an adverse event early in life may increase resilience toward future challenges or, vice versa, enhance vulnerability (Daskalakis et al., 2013).

Apart from that, housing conditions may be an important environmental factor. Mice in our study were housed in individually ventilated cages (IVC) until adulthood, which has been previously shown to mask behavioral changes in a genetic model of schizophrenia (Logge et al., 2014). Similarly, an enriched environment in the first month of life prevented some deficits induced by the MAM model in rats (Zhu & Grace, 2021). Mueller and colleagues looked at the difference between open caging and IVC systems. They showed that poly(I:C) at a dose of 5 mg/kg caused a high number of abortions, and at a dose of 1 mg/kg, no behavioral disruptions in IVC mice, while equal doses in open-cage-housed animals resulted in behavioral alterations (Mueller et al., 2018). Because we only found a behavioral difference between groups in set-shifting, we hypothesize that it is a highly sensitive task with regard to prefrontal alterations and can uncover even subtle neurobiological disruptions.

Furthermore, we found a decreased number of parvalbumin-positive interneurons in the CA1 and CA3 areas of the hippocampus of a group that underwent mild chronic stress but with no effect of poly(I:C). Interestingly, further analysis by sex showed that the effect was mediated solely by female mice. Unstressed female mice had a significantly higher number of PVIs in the CA1 and CA3 compared to stressed female mice, and they also had the highest number of PVIs overall. Both stressed and non-stressed male mice had approximately the same number of PVIs as stressed female mice. Sex differences in the number of PVIs resulting from chronic stress may be underlined by the role of sex steroid hormones and the different developmental trajectories of PVIs in the hippocampus of male and female mice (Wu et al., 2014). Also, our results are in line with findings of decreased number of parvalbumin and somatostatin-positive interneurons, as well as lower parvalbumin and somatostatin mRNA expression in the hippocampus of patients with schizophrenia (Konradi et al., 2011) and an effect of chronic stress on PVIs in all areas of the dorsal hippocampus (Czéh et al., 2015). On the other hand, Giovanoli et al. (2013) found no effect of prenatal immune activation, stress, or their combination on the number of PVIs in the dorsal hippocampus. However, they used a lower dose of poly(I:C) (1mg/kg).

Cortical and subcortical PVIs have a significant role in several cognitive processes. PVIs in the prefrontal cortex have been previously shown to be important for spatial working memory, and their disruption may underly the cognitive deficits seen in schizophrenia (Murray et al., 2015). Here we point toward the impact of chronic stress on hippocampal PVIs.

Acute and chronic administration of D2/D3 agonist quinpirole and 5-HT1A/5-HT7 agonist 8-OH-DPAT produces hyperlocomotion and impairs spatial learning in the Active Allothetic Place Avoidance task in rats.

Chronic administration of D2/D3 receptor agonist quinpirole and serotonin 1A/7 agonist 8-OH-DPAT have been described to produce behavioral alterations in rats relevant to obsessive-compulsive disorder. Both substances resulted in hyperlocomotion, specific „checking“ of objects distributed in the open field and reversal learning impairment (Alkhatib et al., 2013; Hatalova et al., 2014b, 2017; Szechtman et al., 1998, 1999). Our study attempted to replicate the quinpirole and 8-OH-DPAT pharmacological models relevant to OCD and examine spatial learning and cognitive flexibility in a dynamic environment. Furthermore, we tested if pretreatment with glutamatergic agents, memantine and riluzole, would alleviate the cognitive deficits.

We found that repeated treatment with quinpirole (0.25 mg/kg) and acute treatment with 8-OH-DPAT (0.25 mg/kg) produced significant hyperlocomotion in Long-Evans rats. Furthermore, the treatment with both drugs impaired spatial learning in the AAPA in a rotating arena, where rats had to avoid an invisible „shock“ sector with the help of spatial cues. Surprisingly, the administration of quinpirole and 8-OH-DPAT impaired spatial learning so much that reversal couldn't be tested. In addition, rats that received 8-OH-DPAT did not accelerate the escape reaction throughout the training as did the control groups. Visual inspection of their reaction revealed they had intact responsiveness to electrical shocks, but their escape route was less spatially organized, so they were less able to leave the "shock" sector quickly. It also suggests poor spatial knowledge of the environment. Importantly, the correlation between the number of entrances into the „shock“ sector and locomotion in the quinpirole study was significant only for a quinpirole group pretreated with riluzole (1mg/kg), suggesting that a high number of errors in all other groups was not just a byproduct of hyperlocomotion. Similarly, in the 8-OH-DPAT study, the animals acutely treated with 8-OH-DPAT had more entrances to the „shock“ sector per unit of distance, suggesting that the spatial impairment was largely independent of hyperlocomotion.

Interestingly, we observed just the acute effect of 8-OH-DPAT. Only the 8-OH-DPAT (0.25 mg/kg) injection during both habituation/sensitization and acquisition phases increased locomotion and impaired learning. If the drug application was discontinued after the habituation phase, previous sensitization to 8-OH-DPAT did not affect spatial performance and locomotion during acquisition. In contrast, chronic administration of 8-OH-DPAT at low doses (0.0625, 0.125 mg/kg) per 8 days produced hyperlocomotion and compulsive checking even after several days without the 8-OH-DPAT (Johnson & Szechtman, 2016). However, it was tested in the open field, so the difference between spontaneous and motivated behavior might explain the diverging results. Furthermore, we tested the locomotion and cognitive skills, not the manifestation of the compulsion-like behavior per se (checking).

Although spatial learning and memory impairment have also been described in rats subjected to quinpirole treatment in the postnatal period (PD 1-21) (Vorhees & Williams, 2006), as well as in zebrafish (Nabinger et al., 2021), the findings of this work contrast with previous studies from our lab, that showed no effect of quinpirole on initial acquisition learning in the rotating arena even with higher doses (Hatalova et al., 2014, 2017; Stuchlik et al., 2007). Also, no effect of quinpirole on novel object recognition was documented

(de Lima et al., 2011). Different experimental schedules might explain the discrepancy, as the rats in previous studies were introduced to the testing environment 20-30 minutes after the application of quinpirole. In contrast, in the current study, the rats were placed into the arena right after the injection and monitored for 50 minutes. However, although the number of entrances decreased during the 50-minute session in the quinpirole group, it remained still relatively high even in the last 20-30 minutes. Possibly, spending the entire sensitizing experience under quinpirole in a novel environment might be detrimental to spatial learning in that environment.

8-OH-DPAT has been found to impair spatial learning in previous studies (Carli et al., 1995; Jeltsch et al., 2004; Kant et al., 1998), although, in some, it had no effect (Buhot et al., 1995). Also, local microinfusion of 8-OH-DPAT to the medial septum was shown to impair learning in the MWM when injected 10 minutes before the learning (Koenig et al., 2008) and spatial memory in the 8-arm radial maze when injected into the dorsal hippocampus 15 minutes before the task (Egashira et al., 2006). These results suggest an important role of septal 5-HT1A receptors in memory encoding and consolidation (Koenig et al., 2008) and may clarify the mechanism under severe memory impairment found in our study. However, it must be noted that systemic application may affect multiple neural systems in the brain, and the exact mechanism is, therefore, harder to interpret (Warburton et al., 1997).

Memantine and riluzole aggravate cognitive deficits produced by quinpirole and 8-OH-DPAT administration.

We further tested the effect of antiglutamatergic agents, memantine and riluzole, on cognitive performance in quinpirole and 8-OH-DPAT-treated rats. The rats, already sensitized with quinpirole or 8-OH-DPAT and habituated to the testing environment, were injected with memantine or riluzole 30 minutes before the acquisition of the AAPA. In the quinpirole study, memantine and riluzole were injected at the dose of 1mg/kg or 5mg/kg, while in the 8-OH-DPAT study, only the dose of 1mg/kg was used. Memantine is a non-competitive low-affinity NMDA receptor antagonist used mainly in the treatment of Alzheimer's disease. It has been shown to block the NMDA glutamate receptors and normalize the glutamatergic system when over-activated (Olivares et al., 2012). Riluzole, which is currently used in the treatment of amyotrophic lateral sclerosis, inhibits glutamate release and potentiates the reuptake of extrasynaptic glutamate (Frizzo et al., 2004; Fumagalli et al., 2008). Notably, both drugs have promising results in augmentation therapy

in OCD patients (Coric et al., 2005; Ghaleiha et al., 2013; Modarresi et al., 2018; Pittenger et al., 2008).

In our study, neither memantine nor riluzole alleviated the deficit in spatial learning induced by quinpirole and 8-OH-PAT. Memantine at the dose of 5mg/kg significantly aggravated the deficit caused by quinpirole, and both memantine and riluzole (1mg/kg) further exacerbated the learning deficit caused by 8-OH-DPAT, as well as hyperlocomotion. Importantly, the detrimental effect was caused by the interaction of memantine and riluzole with the quinpirole or 8-OH-DPAT, as no such effect of memantine or riluzole was observed in saline groups. On the other hand, the saline group pretreated with riluzole (but also OH-SAL group) had slightly less entranced to the to-be-avoided sector when controlled for locomotion compared to all the other groups.

In the quinpirole study, the findings might be explained by the variable effect of quinpirole on glutamatergic neurotransmission in different structures. While it has been found to increase glutamatergic neurotransmission in some areas, such as substantia nigra (Abarca et al., 1995) or basolateral amygdala (Sun et al., 2019), it was shown to decrease glutamate concentration in the nucleus accumbens (Escobar et al., 2015; Krügel et al., 2004) and medial prefrontal cortex (Sun et al., 2019). NAc is an essential structure for declarative memory formation (Day et al., 2007), as well as reversal learning (Cools et al., 2009) and lesions of NAc have been found to result in stereotypical behavior (Dvorkin et al., 2010). Therefore, drugs decreasing glutamatergic neurotransmission may not only normalize glutamate levels in areas where its concentration is higher but also lead to further decrease in areas with already lower levels, like NAc, and contribute to even more severe disruption of the system.

One of the possible explanations of the potentiated effect of 8-OH-DPAT with memantine and riluzole may be their action upon different brain structures. 8-OH-DPAT seems to presynaptically block AMPA receptors and glutamate release in the CA1-CA3 region of the hippocampus through 5-HT1A receptors (Costa et al., 2012). Activation of 5-HT1A receptors has also been shown to inhibit long-term potentiation (LTP) in the hippocampus, which is thought to have an essential role in learning and memory (reviewed, for example, in Nicoll, 2017). Besides the hippocampus, 8-OH-DPAT reduces excitation in the entorhinal cortex, and 5-HT1A and 5-HT7 receptors inhibit glutamate transmission in the frontal cortex, cerebellum and many other structures involved in affective and motor behavior (reviewed in Ciranna, 2006). Therefore, 8-OH-DPAT may impair learning and

memory by inhibiting LTP through 5-HT1A activation, and memantine and riluzole may disturb it further by decreasing glutamate levels.

It is also possible that glutamatergic treatments are effective only in specific subtypes of patients, as proposed by Vček et al. (2018). A recent study used fMRI to look at the effect of memantine in rat quinpirole model and showed that memantine increased activity in the frontal cortex in saline control animals, while it had no such effect in quinpirole-treated rats. These findings again point toward the interaction between dopaminergic and glutamatergic receptors and suggest that glutamatergic treatment might be unsuitable for patients with altered dopaminergic neurotransmission (Straathof et al., 2022). Also, both memantine and riluzole have been found effective only in augmentation therapy together with other, mainly SSRI, medication (Ghaleiha et al., 2013; Modarresi et al., 2018; Pasquini & Biondi, 2006; Pittenger et al., 2008; Poyurovsky et al., 2005; Stewart et al., 2010), although those studies assessed especially the OCD symptoms and not executive functions. Interestingly, a study on rats by Wesierska et al. (2019) found an enhancing effect of memantine on spatial learning and memory in the AAPA task, which is in contrast with our results that showed no beneficial effect of memantine in the same task.

In conclusion, 8-OH-DPAT and quinpirole sensitization probably influence glutamatergic neurotransmission through different pathways and induce a decrease of glutamatergic neurotransmission in the hippocampus, which subsequently impairs learning and memory. Memantine and riluzole interact with quinpirole and 8-OH-DPAT to produce further deficits that are not seen when both drugs are administered alone.

CRNP2 knockout in mice produces behavioral deficits and neuronal alterations similar to those in ASD patients.

Disruption in proteins involved in neurodevelopmental processes (e.g., axon growth, guidance and pruning) is implicated in neurodevelopmental disorders, such as autism spectrum disorder or schizophrenia (reviewed in Arnold et al., 2005; Kumar et al., 2019). Collapsin response mediator protein 2 (CRMP2) has a role in regulating axon guidance by mediating semaphorin 3A signaling and its defect has been associated mainly with ASD and schizophrenia, but also with other conditions like epilepsy, mood disorders or Alzheimer's disease (Braunschweig et al., 2013; Clark et al., 2006; De Rubeis et al., 2014; Liu et al., 2014; Nakata et al., 2003; Quach et al., 2015). To examine its role in these conditions and neurodevelopmental processes, newly generated CRMP2 full knockout mice (crmp2 -/-)

were developed in the Laboratory of Molecular Neurobiology at the Institute of Physiology CAS (as described in Žiak et al., 2020).

We showed that CRMP2 knockout (KO) mice display decreased social interaction in juvenile age and decreased sociability in adulthood. While there was no difference between groups in ultrasonic vocalization during 5-minute isolation on PD6, knockout mice vocalized significantly less than wild-type (WT) mice on PD8, and on PD12, they almost stopped vocalizing at all. Moreover, the social impairment of CRMP2 KO mice lasted into adulthood, when they did not show a preference for a social partner in the three-chamber test, although they had preserved social novelty. Furthermore, we found decreased spontaneous alternation in knockouts. Although both groups had similar exploratory activity in the Y-maze, CRMP2 KO had a significantly decreased ratio of spontaneous arm alteration, suggesting increased perseveration or, possibly, working memory impairment. On the other hand, long-term memory and reversal learning were intact in CRMP2 KO mice, as shown by a normal performance in the AAPA in a rotating arena. CRMP2 KO mice also showed decreased anxiety in adulthood in the Elevated Plus Maze (EPM). They spent more time in open arms, visited them more often, and were more active in the maze than the WT mice.

Furthermore, CRMP2 has been shown to mediate not only Sema3A signaling implicated in axon guidance but also Sema3F signaling important for postnatal axon and dendritic spine remodeling. CRMP2 knockout mice had defects in axonal guidance, pruning and dendritic spine remodeling in multiple areas of the CNS. Importantly, changes in both Sema3A and Sema3F signaling pathways have been implicated in ASD pathogenesis (Calderon de Anda et al., 2012; Degano et al., 2009; Li et al., 2019; reviewed in Carulli et al., 2021). It is in line with behavioral results showing impairments in social communication in juvenile mice, which resembles impaired social interaction in ASD that typically develops in the first three years of life and is considered one of the key diagnostic criteria of ASD (WHO, 2019).

Interestingly, we found no impairment in cognitive flexibility as measured by spatial reversal learning in the AAPA tasks. In contrast with the apparent tendency to rigidity displayed by people with ASD in everyday life, studies on executive cognitive flexibility showed contrasting results. Some studies reported deficits in set-shifting tasks (Brady et al., 2013; Miller et al., 2015; Yerys et al., 2009), while others showed ASD patients had normal performance when controlled for IQ (de Vries & Geurts, 2012; Di Sarro et al., 2022; Dirks et al., 2020; Yerys et al., 2015). Unfortunately, the studies use different tasks to measure cognitive flexibility, making the interpretation challenging. Some authors suggested that

people with ASD might be more impaired in cognitive flexibility tasks under specific conditions, especially in tasks with less predictable changes or when explicit instructions are not provided (Van Eylen et al. 2011). It is, therefore, possible that even in rodent models with high face and construct validity regarding ASD, deficits in cognitive flexibility may not be detected. On the other hand, cognitive flexibility impairment has been shown in several other genetic (and nongenetic) rodent models relevant to ASD (as described in Chapter 5.3.1). However, in a subset of studies, decreased cognitive flexibility might be related to a broader learning/memory impairment, which was not detected in CRMP2 knockouts.

6 Conclusion

In the present work, we studied (spatial) cognitive flexibility and other behavioral characteristics in several rodent models relevant to schizophrenia, obsessive-compulsive disorder, and autism spectrum disorder. In a two-hit mice model of schizophrenia, we found the only between-group difference in set-shifting (induced by MIA) and decreased number of PVIs in the hippocampus of stressed female mice. We showed that set-shifting seems to be a highly sensitive task with regard to prefrontal alterations and can uncover even subtle neurobiological disruptions. Our results also point toward the impact of chronic stress on hippocampal PVIs and their possible role in pathological processes. Notably, the relationship between several negative or stressful life events might be more complicated, and adversity can sometimes increase resilience instead of vulnerability toward further stressors. Therefore, rodent two-hit or multiple-hit models may be important tools for studying the interaction between genetic and environmental factors and for elucidating why psychiatric symptoms develop in some individuals but not in others.

In pharmacological rat models relevant to OCD, we showed that sensitization to quinpirole and 8-OH-DPAT produces severe impairment in spatial learning and memory, probably induced by changes in glutamatergic neurotransmission. However, drugs decreasing glutamatergic neurotransmission, memantine and riluzole, further impaired the performance in a spatial memory task in both models. Because no such effect was seen when administered alone, memantine and riluzole probably interacted with quinpirole and 8-OHDPAT. The results suggest an interaction between the glutamatergic, dopaminergic, and serotoninergic systems, which should be considered when choosing pharmacological treatment.

Lastly, we showed that CRMP2 has a role in both Sema3A and Sema3F signaling, and its knockout produces both behavioral and neurobiological impairments relevant to autism spectrum disorder. CRMP2 knockout mice had defects in axonal guidance, pruning and dendritic spine remodeling. Furthermore, we found decreased social interaction (fewer USV calls) in pups, which is in line with impaired social interaction in ASD early in life. Importantly, reduced sociability endured into adulthood, as adult CRMP2 knockouts showed no preference for a social partner in the three-chamber test. Moreover, CRMP2 knockouts had increased perseveration in the Y-maze and decreased anxiety in the EPM. Interestingly, we found no impairment in cognitive flexibility. Also, spatial learning and long-term memory were preserved, suggesting no severe cognitive deficit. In conclusion, the disruption

of CRMP2 seems to be an important factor in ASD pathophysiology, and CRMP2 knockout mice are a promising model for exploring neurobiological mechanisms.

7 Summary in Czech

7.1 Kognitivní flexibilita v myším „two hit“ modelu schizofrenie a role parvalbumin-pozitivních interneuronů

V této studii jsme se zaměřili na prozkoumání behaviorálních deficitů a změn v parvalbumin-pozitivních interneuronech (PVIs) v myším „two-hit“ modelu schizofrenie. Nejprve jsme aplikovali poly(I:C) březím samicím, jejichž mláďata dále podstoupila stresování v období adolescence. Zjistili jsme deficit v prostorové verzi *set-shiftingu* ve skupině, která byla vystavena poly(I:C) v prenatálním období, zatímco v žádné další úloze (prepulzní inhibice, senzitivita na amphetamin, lokomoce v open fieldu, úzkost v EPM) se skupiny nelišily. Analýza dále ukázala snížený počet PVIs v dorzálním hipokampu u samic, které prošly stresováním ve srovnání se samicemi, které stresováním neprošly. Výsledky naší studie ukázaly, že set-shifting může být považován za vysoce senzitivní úlohu ve vztahu k prefrontálním deficitům, která je schopná odhalit i malé změny, jež se v jiných úlohách neprojeví. Poukázaly také na efekt opakovaného, nepředvídatelného stresu na pokles PVIs v hipokampu, zejména u samic.

7.2 Efekt látek snižujících glutamátergní neurotransmisi na kognitivní deficit v potkaních modelech obsedantně-kompulzivní poruchy

V této práci jsme sledovali efekt memantinu a riluzolu, léků snižujících glutamátergní neurotransmisi, ve dvou potkaních modelech OCD založených na quinpirolové a 8-OH-DPAT senzitizaci. Opakovaná aplikace quinpirolu a 8-OH-DPAT narušila prostorové učení a paměť v úloze aktivního vyhýbání se místu, a to do takové míry, že nebylo možné testovat reversal. Memantin i riluzol překvapivě ještě prohloubily tento deficit, přestože žádný takový efekt nebyl pozorován v případě, kdy byly aplikovány samostatně. Senzitizace quinpirolem a 8-OH-DPAT pravděpodobně různými cestami ovlivňuje glutamátergní neurotransmisi a vyvolává pokles glutamátu v hipokampu, což následně zhoršuje učení a paměť. Memantin a riluzol interagují s quinpirolem a 8-OH-DPAT, čímž dochází k dalšímu prohloubení kognitivního deficitu, který se neprojevuje v případě samostatného podání obou léčiv.

7.3 Role CRMP2 v neurovývoji a jeho význam v rozvoji poruch autistického spektra

V této studii jsme se zaměřili na roli collapsin response mediator proteinu 2 (CRMP2) v neurovývoji a na jeho potencionální roli v rozvoji neurovývojových onemocnění, zejména poruchy autistického spektra. V laboratoři Molekulární Biologie ve Fyziologickém ústavu AV ČR byly vyvinuty myši s delecí CRMP2, u kterých se ukázaly neurovývojové i behaviorální abnormality. CRMP2 knockouti měli sníženou sociální interakci a snížená sociabilita přetrvala až do dospělosti, kdy nevykazovali preferenci pro sociálního partnera v three-chamber testu. Kromě toho měli zvýšenou perseveraci ve Y-maze a nižší úzkost v EPM. Překvapivě jsme nezjistili žádné zhoršení v kognitivní flexibilitě. Nebyly však porušeny ani další kognitivní funkce, jako dlouhodobá paměť a prostorové učení. Dále se ukázalo, že CRMP2 má důležitou roli v Sema3A a Sema3F signalizaci a s tím souvisejícím navádění axonů, prořezávání a remodelaci dendritických trnů, které byly u CRMP2 knockoutů pozměněné. Lze tedy říci, že narušení CRMP2 se zdá být důležitým faktorem v patofyziologii poruch autistického spektra.

8 Summary in English

8.1 Cognitive flexibility in the mice two-hit model relevant to schizophrenia and the role of parvalbumin-positive interneurons

In this study, we aimed to investigate behavioral deficits and changes in parvalbumin-positive interneurons (PVIs) in a two-hit model of schizophrenia. We first administered poly(I:C) to pregnant mice whose offspring underwent stress in periadolescence. We found a deficit in the spatial version of set-shifting in the group exposed to poly(I:C) in the prenatal period. However, the groups did not differ in other behavioral tasks (prepulse inhibition, amphetamine sensitivity, locomotion in the open field, anxiety in the EPM). The analysis further showed a reduced number of PVIs in the dorsal hippocampus of females who underwent stress compared to females in the control group. Our study showed that set-shifting could be considered a highly sensitive task in relation to prefrontal deficits, capable of detecting even small changes that are not apparent in other tasks. Our results also pointed to the effect of chronic, unpredictable stress on the reduction of PVIs in the hippocampus, especially in female mice.

8.2 Effect of antiglutamatergic agents, memantine and riluzole, on the cognitive deficit in rat model relevant to obsessive-compulsive disorder

In the present study, we looked at the effect of memantine and riluzole, drugs decreasing glutamatergic neurotransmission, in two rat models relevant to obsessive-compulsive disorder. We used repeated administration of quinpirole and 8-OH-DPAT and showed that it impaired spatial learning and memory in the Active Allothetic Place Avoidance task. The impairment was so severe that the reversal couldn't be tested. Surprisingly, memantine and riluzole exacerbated this deficit, although no such effect was observed when they were applied alone. Sensitization with quinpirole and 8-OH-DPAT likely affect glutamatergic neurotransmission through different pathways and decrease hippocampal glutamate transmission, which subsequently impairs learning and memory. Memantine and riluzole interact with quinpirole and 8-OH-DPAT to cause additional deficits that do not manifest when the two drugs are administered alone.

8.3 The role of CRMP2 in neurodevelopment and its relevance for autism spectrum disorder

In this study, we focused on the role of collapsin response mediator protein 2 (CRMP2) in neurodevelopment and its potential function in neurodevelopmental disorders, particularly autism spectrum disorder. Mice with CRMP2 deletion were developed in the Laboratory of Molecular Biology at the Institute of Physiology CAS and indeed showed neurodevelopmental and behavioral abnormalities. CRMP2 knockouts had reduced social interaction, and the reduced sociability persisted into adulthood when they showed no preference for a social partner in the three-chamber test. In addition, they had decreased spontaneous alternation in the Y-maze and anxiety in the EPM. Surprisingly, we found no impairment in cognitive flexibility. However, other cognitive functions, such as long-term memory and spatial learning, were not impaired either. Furthermore, CRMP2 appeared to have an important role in Sema3A and Sema3F signaling and associated axon guidance, pruning and dendritic spine remodeling, which were altered in CRMP2 knockouts. It can be concluded that CRMP2 disruption appears to be an important factor in the pathophysiology of autism spectrum disorder.

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10 Publications

Publications relevant to the thesis

Maleninska, K., Janikova, M., Radostova, D., Vojtechova, I., Petrasek, T., Kirdajova, D., Anderova, M., Svoboda, J., Stuchlik, A. (2022). Selective deficits in attentional set-shifting in mice induced by maternal immune activation with poly(I:C), *Behavioural Brain Research 419*, 113678. https://doi.org/10.1016/j.bbr.2021.113678.
IF2022–2023 = 3.352

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Publications not directly relevant to the thesis

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11 Appendix

1) Maleninska, K., Janikova, M., Radostova, D., Vojtechova, I., Petrasek, T., Kirdajova, D., Anderova, M., Svoboda, J., Stuchlik, A. (2022). Selective deficits in attentional set-shifting in mice induced by maternal immune activation with poly(I:C), *Behavioural Brain Research 419*, 113678. https://doi.org/10.1016/j.bbr.2021.113678.

2) Janikova, M., Brozka, H., Radostova, D., Svoboda, J. & Stuchlik, A. (2019). No effect of riluzole and memantine on learning deficit following quinpirole sensitization – An animal model of obsessive-compulsive disorder. *Physiology & Behavior, 204*, 241-247. https://doi.org/10.1016/j.physbeh.2019.01.013

3) Janikova, M., Mainerova, K., Vojtechova, I., Petrasek, T., Svoboda, J., Stuchlik, A. (2021). Memantine and Riluzole Exacerbate, Rather Than Ameliorate Behavioral Deficits Induced by 8-OH-DPAT Sensitization in a Spatial Task. *Biomolecules, 11(7)*, 1007. https://doi.org/10.3390/biom11071007

4) Ziak, J., Weissova, R., Jerabkova, K., Janikova, M., Maimon, R, Petrasek T. et al. (2020). CRMP2 mediates Sema3F-dependent axon pruning and dendritic spine remodeling. *EMBO reports, 21*(3), e48512. https://doi.org/10.15252/embr.201948512