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# Effects of methylphenidate on the behavior of male 5xFAD mice

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ABSTRACT

Alzheimer's disease is a neurodegenerative disorder characterized by a loss of memory and spatial orientation. It is also reported that the dopamine system is affected. Dopamine plays a prominent role in motor functions, motivation, emotion, arousal and reward, and it is important for learning and memory. One model that represents characteristic hallmarks of Alzheimer's disease is the 5xFAD mouse model, in which parenchymal plaque load starts at 2 months of age. Transgenic 5xFAD mice show the first behavioral deficits at 6 months, which are evident at 9 months of age. In this study, we investigated the pharmacological influence of methylphenidate (MPH) on behavioral deficits of 5xFAD mice. Using a battery of behavioral tests, we observed no influence of MPH on anxiety in the elevated plus maze, whereas the locomotion and explorative activity in the open field was increased in transgenic and non-transgenic 5xFAD mice after the application of MPH. Further MPH inhibits habituation in the open field in healthy 5xFAD littermates after the application of 10 mg/kg MPH. On the other hand, 10 mg/kg MPH improved spatial memory in 6-month-old transgenic 5xFAD males, i.e., at a time point when deficits start to occur. However, in 9-month-old transgenic mice, MPH did not improve persisting learning and memory deficits. We concluded that MPH might improve the non-cognitive, apathy-like behavior (indicated by a reduced exploration), but it has no influence on sustained Alzheimer typical learning and memory deficits.
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## 1. Introduction

Morbus Alzheimer is a neurodegenerative disease characterized by a decline of learning and memory performance and by depression, agitation, apathy and mood disturbances (Houghton and Howes, 2005). Several neurotransmitter and modulator systems are also changed in Alzheimer's disease (Selkoe, 1991). Although the cholinergic system shows the highest abnormality, other transmitters such as glutamate, GABA and monoamines like norepinephrine, serotonin and dopamine (Reinikainen et al., 1990; Selkoe, 1991; Houghton and Howes, 2005) are affected too. The dopamine concentration in the temporal and hippocampal cortex, as well as in the hippocampus, is decreased by 18–27% in the brains of Alzheimer patients (Reinikainen et al., 1990). In 1982, Marchbanks (1982) reported a deficit of catecholamines and a reduced level of β-hydroxylase, which leads to a noradrenergic loss.

Dopamine plays a role in different brain systems. The mesocorticolimbic dopamine system is important for addiction, depression and schizophrenia, and it is involved in the regulation of emotions and reward (Van den Heuvel and Pasterkamp, 2008) as well as in processes of learning and memory consolidation (Matthies, 1989; Schultz, 1997; Kandel et al., 2000; Reymann and Frey, 2007). Thus, it might be possible to improve learning deficits which typically occur in Alzheimer's disease by the stimulation of the dopaminergic system. Stimulants such as cocaine, amphetamine or methylphenidate (MPH) are valuable drugs for the treatment of different diseases that relate to the dopaminergic system (Han and Gu, 2006). MPH is very often used as therapeutic agent in attention deficit hyperactivity disorder (Balcioglu et al., 2009; Bethancourt et al., 2009) and narcolepsy (Ferreira et al., 2010). Similarly to amphetamine and cocaine (Yano and Steiner, 2007; Dow-Edwards et al., 2008), it stimulates the release of catecholamines and inhibits their reuptake by binding their transporters, especially the dopamine transporter (DAT, Ferreira et al., 2010). Subsequently, extracellular dopamine is increased in the prefrontal cortex (PFC, Koda et al., 2010), in the putamen and nucleus accumbens (nacc, Kuczenski and Segal, 1997), which is linked to reinforcing properties (Ferreira et al., 2010). MPH is successfully used by students in the USA to improve their academic efficiency (Marco et al., 2011; Sadasivan et al., 2012). A positive influence of MPH on behavior could also be demonstrated in single case studies, in which especially apathy, abulia and reluctance were recovered (Galynker et al., 1997). In rodents, MPH increases exploration and locomotion, whereas it decreases anxiety (McFadyen-Leussis et al.,

*Abbreviations:* APP, amyloid precursor protein; AUC, area under curve; CET, Central European Time; DAT, dopamine transporter; DDC, dopamine decarboxylase; FAD, familiar Alzheimer's disease; GABA, gamma-aminobutyric acid; MPH, methylphenidate; Nacc, nucleus accumbens; PFC, prefrontal cortex; PS1, presenilin 1; TH, tyrosine hydroxylase.

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2004; Mioranzza et al., 2010; Niimi et al., 2011). The learning performance in the Morris water maze was also improved by the application of MPH (McFadyen-Leussis et al., 2004). However, there are no reports of the influence of MPH on learning deficits of animal models with Alzheimer's disease. We investigated whether the behavioral deficits in transgenic 5xFAD males could be reduced with the psychostimulant MPH. 5xFAD males were chosen due to their cognitive and non-cognitive deficits at 9 months of age. Transgenic males show a decreased level of anxiety in the elevated plus maze, a reduced locomotion and exploration in the open field, and spatial learning deficits in the Morris water maze, which are described in detail by Schneider et al. (2014).

## 2. Methods

### 2.1. Animals and experimental conditions

The 5xFAD mouse model (Tg6799) was developed by Oakley et al. (2006). This double transgenic mouse overexpresses the amyloid precursor protein (APP) carrying the Swedish (K670N, M671L), Florida (I716V) and London mutation (V717I) as well as the human presenillin-1 (PS1) carrying the M14 6 L and L28 6 V mutations. Mutations are expressed under the control of the murine Thy-1-promotor. Mice from this line have high APP expression correlating with high burden and accelerated accumulation of the 42 amino acid species of beta-amyloid. Only males ($n = 200$) were used for the pharmacological treatment to exclude a possible effect of the estrogen metabolism on dopamine homeostasis (Hruska and Nowak, 1988; Küppers et al., 2000; Johnson et al., 2010). Animals were bred at the German Center of Neurodegenerative Diseases in Magdeburg and kept in groups of maximal five animals in a temperature controlled room at 20 ° C ±2 ° C and a 12/12 h light–dark cycle (light on at 6 a.m.). Food and water were available *ad libitum*. Behavioral experiments were performed between 8:00 a.m. and 5:00 p.m. (CET). All animal procedures have been approved by the ethics committee of the German federal state of Sachsen-Anhalt and are in accordance with the European Communities Council Directive (86/609/EEC).

### 2.2. Substance injection

Methylphenidate (hydrochloride, Sigma) or sodium chloride (NaCl, 0.9%, Braun) as control was injected intraperitoneally to transgenic or non-transgenic littermates 45 min before the respective behavioral test. Methylphenidate was applied in a concentration of 3 mg/kg or 10 mg/kg, respectively. Mice were randomly assigned to one of the experimental or to the control group, and the same drug concentration was given for all experiments. The injection was given once before the elevated plus maze test, then before the first trial of the open field test and before the training days in the Morris water maze (Fig. 1). The behavioral investigations were performed 45 min after the injection, as it was shown that this is a peak of dopamine concentration in response to MPH application (Koda et al., 2010). All mazes except the water maze were cleaned with 70% 2-propanol between the trials.

### 2.3. Elevated plus maze

The elevated plus maze consisted of four cross-shaped arms (28 × 5 cm, height from floor: 60 cm). Two arms facing each other were enclosed on three sides by 15.5 cm high walls, the other two arms, also facing each other, were open. The mouse was placed in the center of the plus maze and allowed to explore the maze for 5 min. The time that the mouse spent in each arm was measured by the program Video Mot2 (Version 5.45, TSE Systems, Bad Homburg, Germany). An increased proportion of time spent in the open arms indicated reduced anxiety. If the mouse fell off an open arm, the trial was stopped and excluded from the analysis.

### 2.4. Open field

Animals were allowed to explore an empty field (40 × 40 × 24 cm) for 5 min without any disturbing factors. The mouse was placed gently in the center of the field. The program Video Mot2 (Version 5.45) was used to measure the patterns of running and rearing as indicators of agility and exploration. Determining habituation in the open field, the distance and rearing measurements were repeated after 4 h (recall) and 24 h (re-recall). To exclude a long-lasting stimulation effect of MPH on the activity after 4 or 24 h in the open field, we measured the activity of transgenic and non-transgenic 5xFAD mice in their home cage after an injection of MPH (see paragraph “Activity in the home cage”).

### 2.5. Morris water maze

In a pool (120 cm in diameter, 60 cm deep) filled with opaque water, mice learned to localize a non-visible platform located 0.5 cm under the

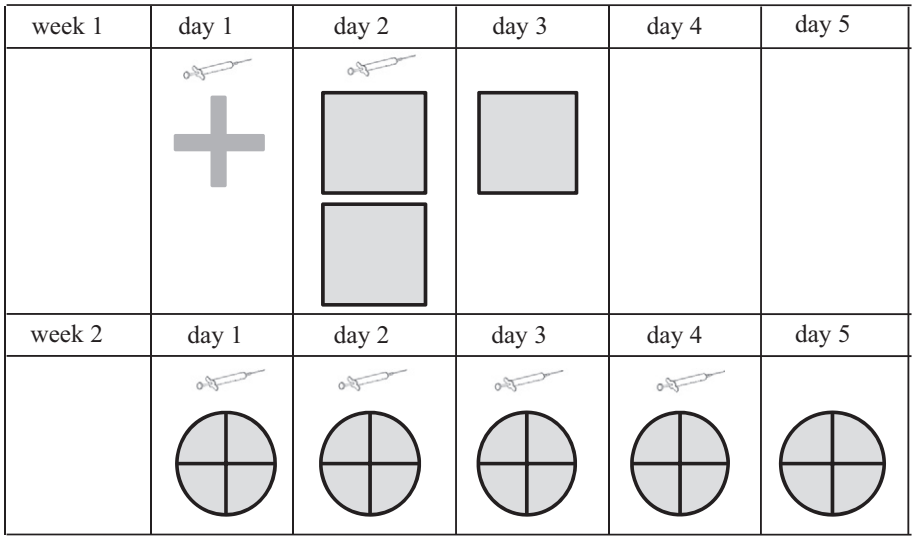


**Fig. 1.** Scheme of the procedure of behavioral tests. At first, the elevated plus maze was done with one injection before the test. Next, the open field test was done with one injection before the first trial. In the second week, the Morris water maze was done with 4 × 4 trials per day and one application each day before the first trial. Each injection was given 45 min before the behavioral test.

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