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**Repeated application of Modafinil and Levodopa reveals a drug-independent precise timing of spatial working memory modulation**

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## Highlights

Modafinil and Levodopa modulate spatial working memory time specifically

The time window is drug independent

Drugs differ in their dose response effects

## Abstract

Cognition enhancing drugs often target the dopaminergic system, which is involved in learning and memory, including working memory that in turn involves mainly the prefrontal cortex and the hippocampus. In most animal models for modulations of working memory animals are pre-trained to a certain criterion and treated then acutely to test drugs effects on working memory. Thus, little is known regarding subchronic or chronic application of cognition enhancing drugs and working memory performance. Therefore we trained male rats over six days in a rewarded alternation test in a T-maze. Rats received daily injections of either modafinil or Levodopa (L-Dopa) at a lower and a higher dose 30 min before training. Levodopa but not modafinil increased working memory performance during early training significantly at day 3 when compared to vehicle controls. Both drugs induced dose dependent differences in working memory with significantly better performance at low doses compared to high doses for modafinil, in contrast to L-Dopa where high dose treated rats performed better than low dose rats. Strikingly, these effects appeared only at day 3 for both drugs, followed by a decline in behavioral performance. Thus, a critical drug independent time window for dopaminergic effects upon working memory could be revealed. Evaluating the underlying mechanisms contributes to the understanding of temporal effects of dopamine on working memory performance.

Keywords: dopamine; working memory; T-maze; cognition.

## Introduction.

Working memory has been defined as “central executive” mechanisms” of cognition relating to temporary storage and operation of information in both, humans and animals, in order to guide future response selection [ 1, 2]. Working memory is essential for facilitating complex behaviors. As such, working memory has become a central construct in cognitive neuroscience. Spatial working memory has been considered as a dynamic encoding process of spatial information over a short time, by acquisition and repeatedly updating of changing spatial information over time [3], thus temporally representing a recently visited place to guide forthcoming behavior. The capacity of spatial working memory can therefore be tested by using tasks with a short delay, such as the delayed alternation task.

Working memory depends on a variety of interconnected brain regions, but most of the research supports the main involvement of the prefrontal cortex (PFC) and the hippocampus [4]. Lesions in the medial PFC (mPFC) and hippocampus result in deficits of working memory in rats [5, 6, 7]. The mPFC is the rodent equivalent of the dorsolateral PFC in primates and human subjects. Humans with lesions, particularly in the dorsolateral PFC or the hippocampus show a severe deficit in spatial working memory [8, 9].

Experimental evidence has been raised that various neurotransmitters, particularly dopamine in both of these brain regions regulate working memory [4, 10, 11 and 12]. Moreover, balanced stimulation of PFC dopamine receptors appears to be necessary for optimal working memory performance in rodents and primates. An inverted U-shaped relation, thus deficits in working memory by either elevated or deficient cortical dopaminergic transmission has been observed [13, 14]. Patients with severe perturbations of this balance like as in neuropsychiatric disorders, such as Parkinson’s or Alzheimer’s disease often manifest working memory disabilities [15, 16].

Levodopa therapy in humans and animal models as well as intranasal dopamine application in had a positive effect by increasing extracellular dopamine levels, not only on related motor dysfunction but also on spatial working and reference memory tasks [16,17,18,19,20], although in some studies no effects of dopaminergic medications on spatial working memory in Parkinson's disease could be determined [21, 22]. A similar effect has been observed after application of other dopamine targeting drugs such as modafinil. Modafinil inhibits the dopamine transporter that facilitates the reuptake of extracellular dopamine in the synapses. Thus, both drugs increase the level of extracellular dopamine though by different mechanisms, diffusion of exogenous dopamine through L-Dopa and inhibition of the reuptake of endogenous dopamine through modafinil. However, the effects of subchronic treatment of these drugs on the repetitive updating of spatial working memory during training is still unclear. Therefore, we investigated the effects of two dopaminergic transmission targeting drugs (modafinil and L-Dopa) on spatial working memory in rats trained over six days in a delayed alternation T-maze task, a commonly used paradigm to assess spatial working memory in rodents [2]. In this task, the animal has to make a alternating choice response between two maze arms to obtain a reward, guided by discrete or spatial cues, the trials separated by a short delay period demanding working memory abilities.

## Methods and Materials

### Subjects

The study was conducted using male Sprague–Dawley rats (12-13 weeks old). They were bred and maintained in cages made of Makrolon filled with autoclaved woodchips in the Core Unit of Biomedical Research, Division of Laboratory Animal Science and Genetics, Medical University of Vienna. One week prior to the behavioral tests animals were moved to a separate experimental room where they lived throughout the experiment. Rats were housed individually in cage at (temperature:  $22 \pm 2^\circ\text{C}$ ; humidity:  $55 \pm 5\%$ ; 12 h artificial light/12 h dark cycle: light on at 7:00 am). The study was carried out according to the guidelines of the Ethics committee, Medical University of Vienna, and were approved by the Federal Ministry of Education, Science and Culture, Austria.

### Apparatus

Working memory tests were carried out in a T- maze made of black acrylic consisting of three arms arranged in a T shape. Each goal arm of the maze was 50 cm long, 10 cm in width and equipped with walls with a height of 25 cm. The central arm was 70 cm long with a 20 cm starting box that could be separated by a guillotine door. At the edge of each goal arm, there was a small cup (to prevent rats from seeing whether the dish was baited) containing highly palatable food pellet (dustless precision pellets, 45 mg, Bio-Serv, Frenchtown, NJ; USA ). A large amount of reward was placed outside both goal arms to mask olfactory cues. The maze was located in the same position in a room with several easily identifiable visual cues, and cleaned with 1% incidin® between each animal in order to remove any olfactory cues. Indirect illumination by

floor positioned lamps directed to the ceiling provided equal light intensities in each arm. Trials were monitored by a camera fixed to ceiling and videos stored at a PC.

## Procedure

### Handling and habituation.

A total of 69 rats were included in the experiment. All the rats were handled for 15 minutes each day for 3 consecutive days before habituation. The body weight of the animals was recorded from first day of handling throughout the experiment. The animals were mildly deprived of food during this period to decrease body weight to 85 % of free feeding weight while the tap water was given ad libitum. The body weight of the animals was maintained to 85% of free feeding weight by providing them with limited amount of pellet daily.

Animals were habituated to a T-maze until they voluntarily ate a piece of pellet placed at the end of each arm. One food reward was provided to rats in the home cage each day for a few days prior to training in order to acclimate the rat to the reward in a familiar environment. Habituation was carried out on the fourth and fifth day of food deprivation. During this habituation period, all animals were allowed a 15-min free exploration of the apparatus, daily for two days to familiarize them with the experimental conditions. On the first day of habituation pellets were kept throughout the maze and on the second day only in the food cups located at the end of both arms. After free exploration of the apparatus the animals were carefully picked up and kept back to home cage.



Drug administration and training.

Two mg or 20 mg/kg of a levodopa and carbidopa (Sigma Aldrich) mixture in a ratio of (4:1) dissolved in saline, or 1 mg and 10 mg/kg of modafinil dissolved in 100 % DMSO were applied with five minutes delays between trials during which rats were placed in a cage. All the drugs and vehicle control (saline and DMSO) were administered intraperitoneally (i.p.) 30 min prior to the start of behavioral testing.

A delayed none matching to place task was performed. Each training session consisted of 10 trials (a forced trial followed by 9 choice trials). To begin a trial, the rat was placed in the starting box for 15 seconds, before the guillotine door separating the starting box from the main alley was raised immediately and opened. In the forced trial, a randomly selected goal arm was blocked by a guillotine door, and a reward was placed in the opposite arm, hence the rats were forced to visit a baited arm.

In choice trials, both arms were accessible, but reward was available only in the arm not entered in the previous trial. In the choice trials 1 through 9, rats had to avoid the arm once visited in a previous trial and select the opposite arm to get reward. The next trial began after an interval of 5 minutes delay. Once the animal has chosen an arm, it was allowed about 10 seconds to consume the pellet. Arm entries were recorded when the whole animal, including the tail tip, was in the arm. If rats selected the un-baited arm, a self-correction procedure was introduced by keeping the baited one still baited until it was visited, giving the rats a chance to shift their choice. Entry into the arm visited in the previous trial was registered as an error of working memory. In addition, the working memory index was calculated (correct choices/total trials).

The experiment continued for six successive days (Days 1-6). After each daily session the animals were given a limited amount of food pellets to maintain body weight until the next T-

maze trial on the following day. All behavioral training/testing was performed during the light phase of the light–dark cycle.

## Statistics

In order to address the high variability in day to day performance in treated rats, a one-way-ANOVA with Tukey post hoc tests was conducted for each day. As an indication of learning linear regression analyses were performed for mean working memory indices and days of training. Border of significance was set a  $p \leq 0.05$ . Given are the arithmetic means and standard errors.

## Results

Strikingly, both extracellular dopamine enhancing substances induced group differences in working memory performances only at day 3, however dose-dependently in a different manner.

### Modafinil

Animals treated with modafinil at both doses did not show a difference compared to DMSO controls at any day (fig. 1). However working memory errors ( $F_{2,31}=3.37$ ,  $p=0.047$ ) and (close to the border of significance) index ( $F_{2,31}=3.16$ ,  $p=0.056$ ) differed at day 3. The post hoc analysis revealed significantly enhanced working memory performance in animals treated with 1mg/lkg bodyweight ( $n=10$ ) as compared to 10mg/kg body weight ( $n=12$ ) treated group ( $p<0.05$ ). Only the vehicle control group ( $n=12$ ) showed a significantly positive linear regression of working memory indices over days indicating a learning improvement during training. A deviation from

the linear model could not be detected (Runs test:  $p=0.90$ ). Whereas both treated groups did not show a constant learning performance over the training procedure.

### L-Dopa

Similar to modafinil effects, group differences could be determined in levodopa treated animals in both, working memory errors ( $F_{2,32}=5.67$ ,  $p=0.007$ ) and indices ( $F_{2,32}=5.67$ ,  $p=0.007$ ) only at day 3. In contrast to modafinil, levodopa induced a better performance in animals treated with a higher dose (20mg/kg body weight,  $n=11$ ) over those treated with a lower dose (2mg/kg body weight,  $n=12$ ). Moreover the high dose group showed better working memory than vehicle treated animals ( $n=12$ ) as revealed by the post hoc tests ( $p<0.05$  both). However, considering the entire training period, again only the vehicle treated group showed a significant linear increase in memory indices (Runs test:  $p=0.70$ ).

Taken together no significant working memory improvement was induced by modafinil but by levodopa. Dose-dependent effects upon working memory were opposite between the two drugs and only effective during the early training. Performance decreased and remained at control levels during late training. Constant day to day improvement over training could be observed only in both vehicle treated groups.

### Discussion

We found a transient increase in working memory performance in L-Dopa but not in modafinil treated rats. Both drugs induce a higher concentration of extracellular dopamine although by different mechanisms. While modafinil blocks the dopamine transporter and thus the reuptake of dopamine in the synapse, levodopa increases the dopamine level just by diffusing into the brain.

Modafinil in addition also targets the noradrenaline and serotonin transporter to a certain extent. These differences in physiological effects may partly explain the differences in the dose effects between the drugs, since a higher concentration of modafinil may also increase the side effects upon the noradrenergic and serotonergic systems that then interfere with each other and impairs the neuromodulatory machinery of working memory circuits. The similar effects at a specific time point during training (day 3) however, point to a common time-dependent underlying mechanism induced by both drugs. Since the common effect is the increase of extracellular dopamine it is feasible that this depends on similar alterations of the dopaminergic system by chronically increased extracellular dopamine levels. A variety of mechanisms are conceivable: dopamine receptor internalization, changes in receptor ligand binding capabilities, differences in the relative activation of different receptor subtypes by the different availability of dopamine. Wang et al. [23] observed increased activation of the protein kinase D1 (PKD1) after acute cocaine exposure (also increasing extracellular dopamine levels) in the rat striatum. PKD1 mediated phosphorylation of the dopamine receptor D1 leads to desensitization or internalization of D1 receptors. Chronic L-Dopa treatment can induce dyskinesia as a result of decreased D1 receptor mediated signalling by receptor internalization [24]. Although we did not observe any motor inabilities, probably by the relative low doses used, a similar process may effect also cognition. Braren et al. [25] found a comparable effect in metamphetamine treated mice in a working memory version of the radial arm maze, an improvement of working memory after a single injection and an impairment after a second injection. Besides a decrease of protein kinase zeta and AMPA receptor GluA2 also D1 was downregulated within the hippocampus. Similarly, D2 receptors show agonist-dependent internalization [26]. In contrast, D4 receptors are resistant to agonist induced receptor internalization and degradation as tested in human cell lines [27]. D3

receptor tolerance by repeated agonist stimulation is realized by changes in receptor confirmation rather than desensitization or internalization [28]. Thus, changes in subtype receptor compositions by these processes can underly the observed dynamic changes in working memory performance, as bidirectional functions of a specific receptor type at different dopamine concentrations as well as synergistic and antagonistic physiological functions of different receptor subtypes has been reported (for a review see Seamans and Yang [11]).

Nonlinear e.g. inverted-U-shaped dose-response profiles of postsynaptic dopamine effects in the prefrontal cortex has been described for working memory [11, 14, 29, 30]. Similar dose-dependent effects of D2 receptors on neuronal plasticity have been described in human motor cortex [31, 32] while D2 was antagonized for L-Dopa stimulation of D1 [33]. Skinbjerg et al. [34] reported a decrease in *in vivo* radio-ligand binding to the dopamine 2 receptor during PET studies after amphetamine induced increased extracellular dopamine for several hours. Induction of long-term depression in the striatum of mice has been shown to be modulated by D2 receptor affinity [35].

Finally, working memory training related changes in neuronal circuits, molecular and dopaminergic processes can time specifically interfere with exogenous interventions of dopamine concentrations [36, 37, 38]. Thus, the present study shows that trainable working memory can be enhanced and disrupted by extracellular dopamine-increasing compounds in precise time windows and partly independent of the substance used. The evaluation of the underlying mechanisms would contribute to the understanding of dopaminergic mechanisms in modulating working memory as well of subchronic effects of dopaminergic cognitive enhancers.

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### Figure Captions

Figure 1 Numbers of working memory errors (upper panel) and working memory indices (middle panel) for Modafinil (left panel) and L-Dopa (right panel) treated rats. Significant differences between groups appear at day 3 for both drugs. a: statistically significant differences of drug treated as compared to vehicle treated rats. b: statistically significant differences between groups treated with high and low doses of the drugs. Statistically significant linear regressions (lower panel) between working memory indices and days of training could be determined only in vehicle treated groups in both experiments, indicating a constant improvement of working memory only in the control groups.