



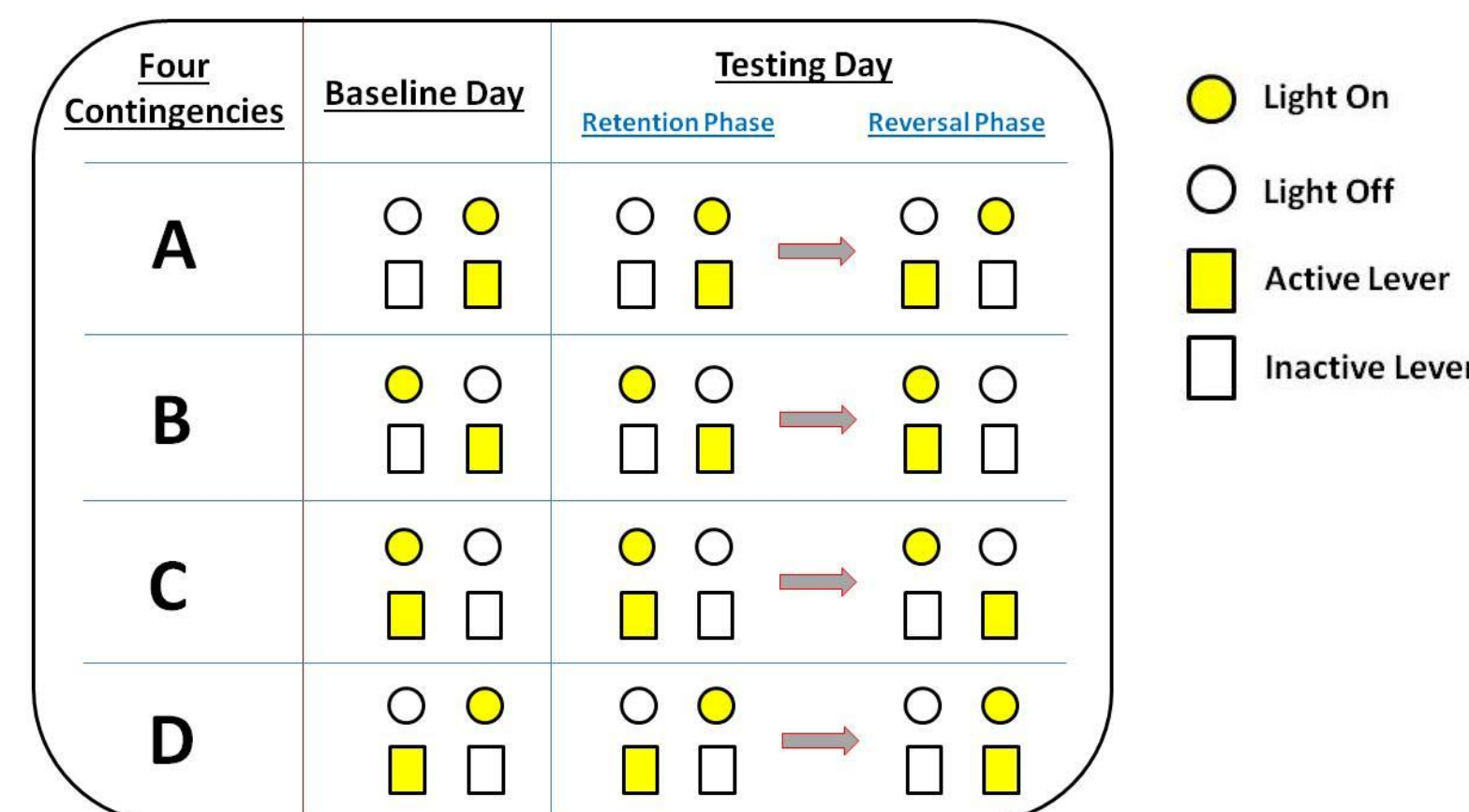
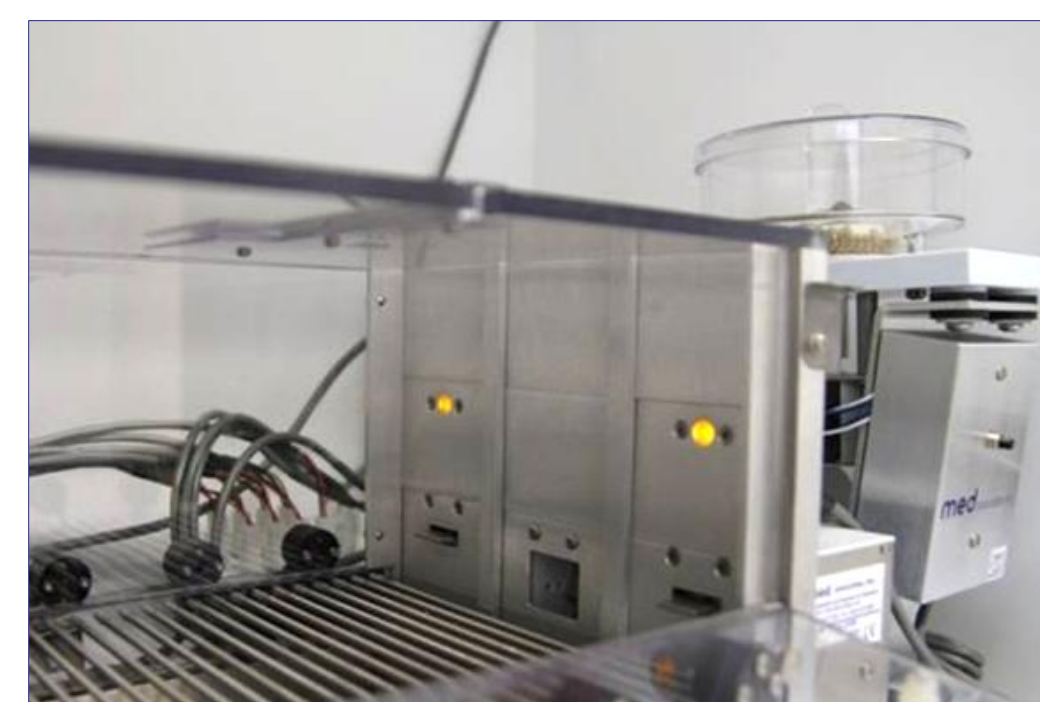
Introduction

Patients with schizophrenia often manifest disruption of executive functions, including behavioral flexibility. Following the “glutamate hypothesis”, which emphasizes the role of glutamate system in schizophrenic neuro-pathology, animal models using the NMDA antagonists such as phencyclidine (PCP) and dizocilpine (MK-801) have been introduced in mimicking specific deficits in executive function and cognition.

Combining with the above models, several behavioral assays are used in testing behavioral deficits and evaluating efficacies of compounds. Among these assays, the serial reversal learning (SRL) test is frequently applied in rodents. In SRL, the animals need to continuously learn the reversed contingencies in order to get reward, making it a perfect tool to study behavioral flexibility.

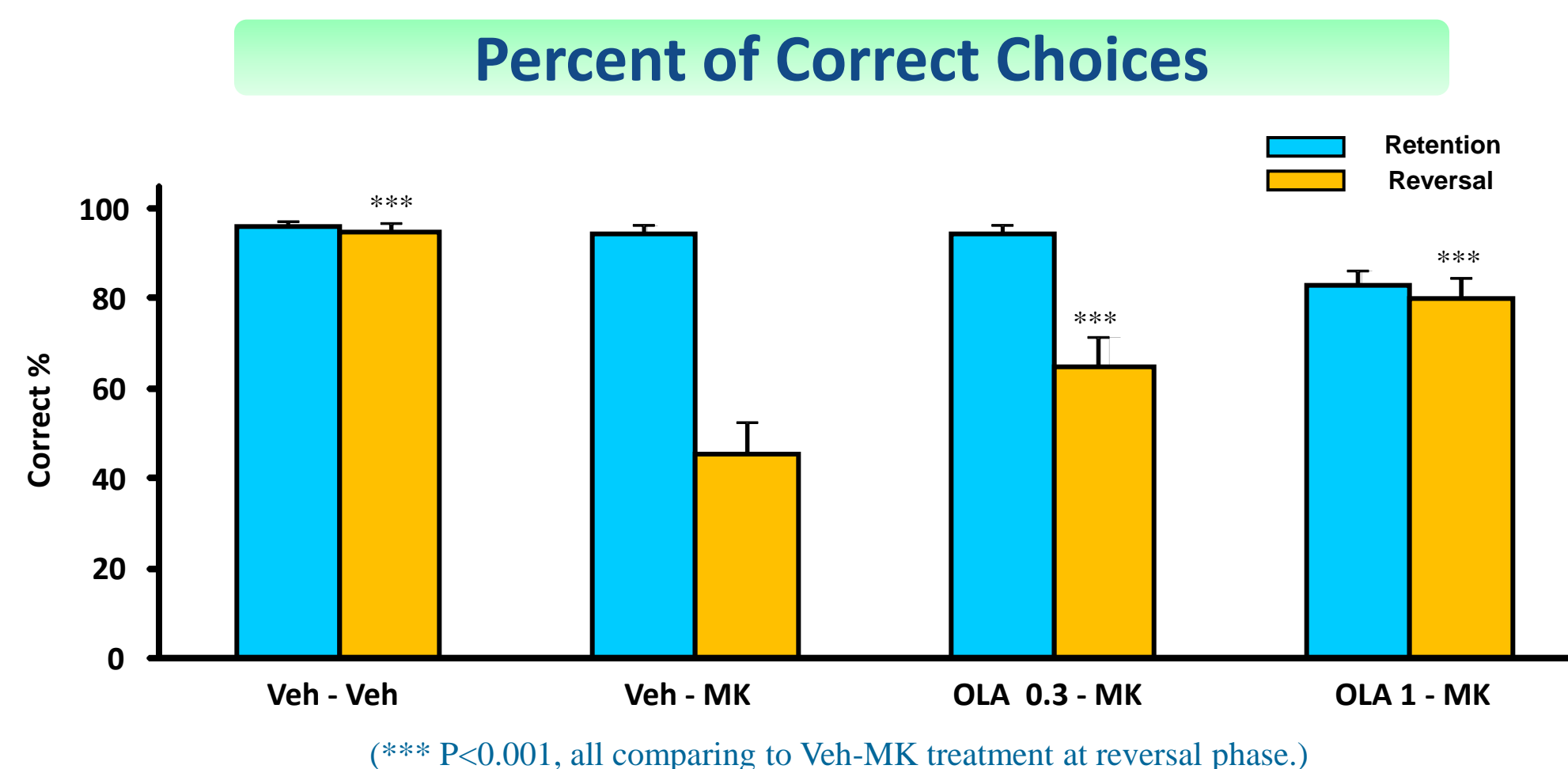
Methods

- Male Long-Evans rats about 320~350 g were used.;
- SRL is a four-stages operant conditioning training, taking 8~10 week to reach testing stage;
- Test compounds in each study were co-administrated with MK-801 0.15mg/kg (same dose in all studies) 30 minutes prior to test session;
- Two-way or one way ANOVA were used for data analysis.

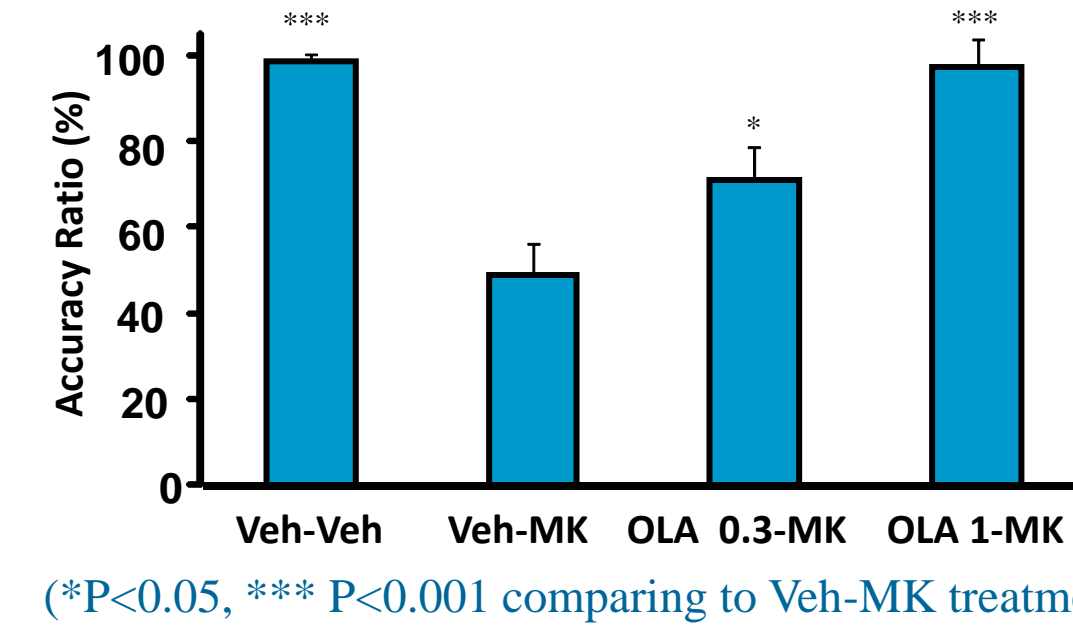


1. Effects of Atypical Antipsychotic Olanzapine

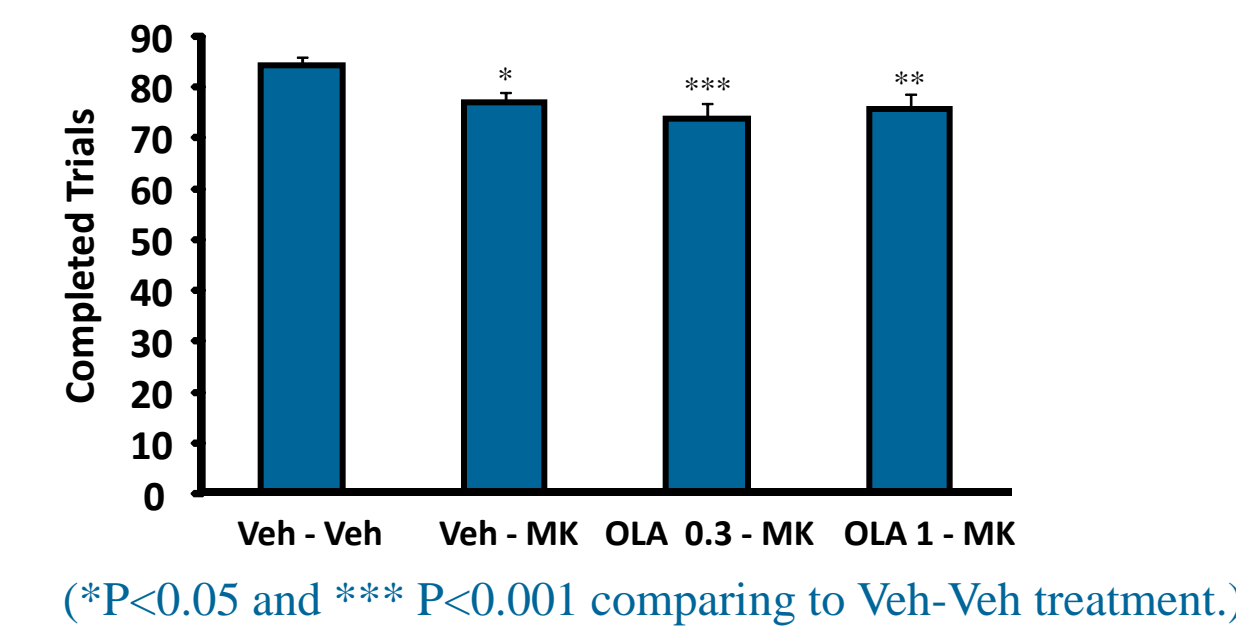
❖ In this Study, the efficacy of olanzapine was evaluated using SRL test. The results showed that olanzapine significantly reversed MK-801-induced deficits in rats.



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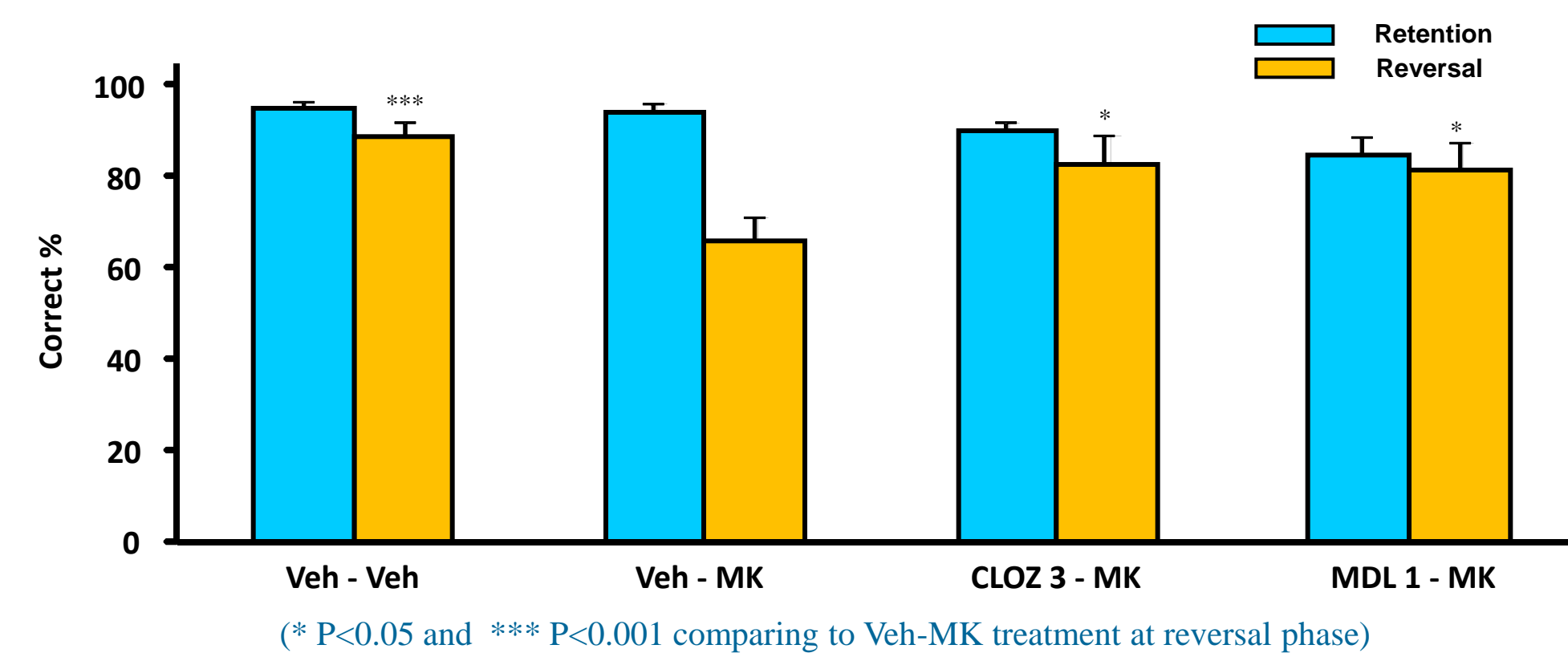
Completed Trials



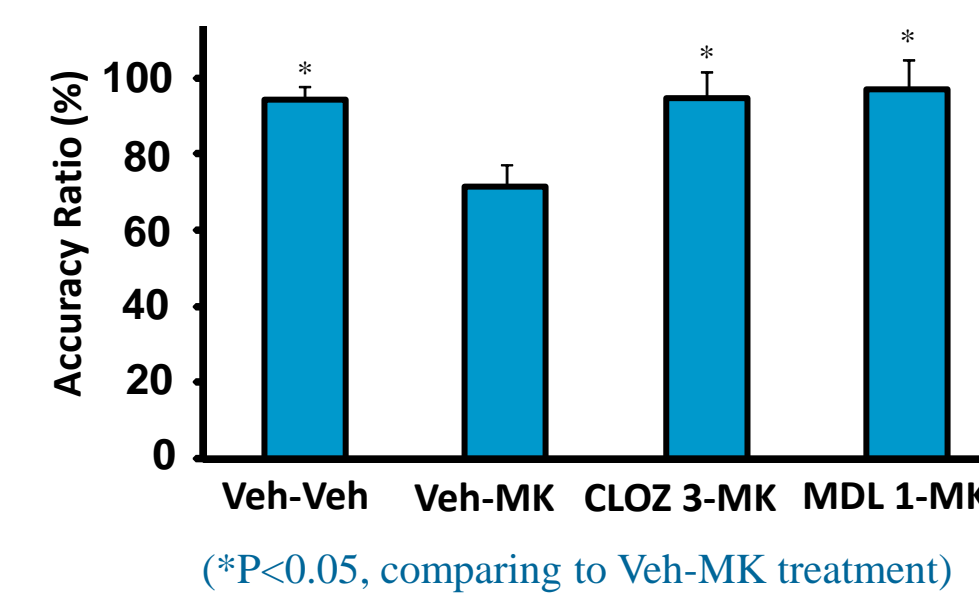
2. Effects of Clozapine and MDL 100907

❖ This study designed to evaluate atypical antipsychotic clozapine 3 mg/kg and an experimental compound MDL 100907 (a 5-HT2A receptor antagonist) 1 mg/kg in SRL test. The results indicated that both compounds significantly saved cognitive flexibility after rats were treated with MK-801.

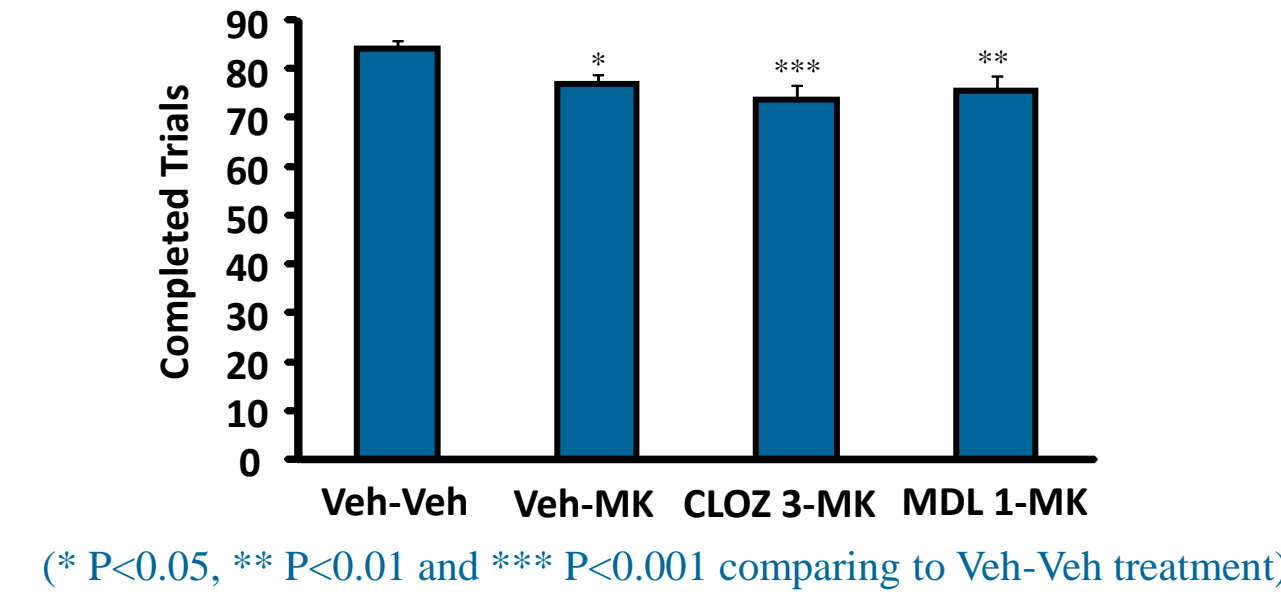
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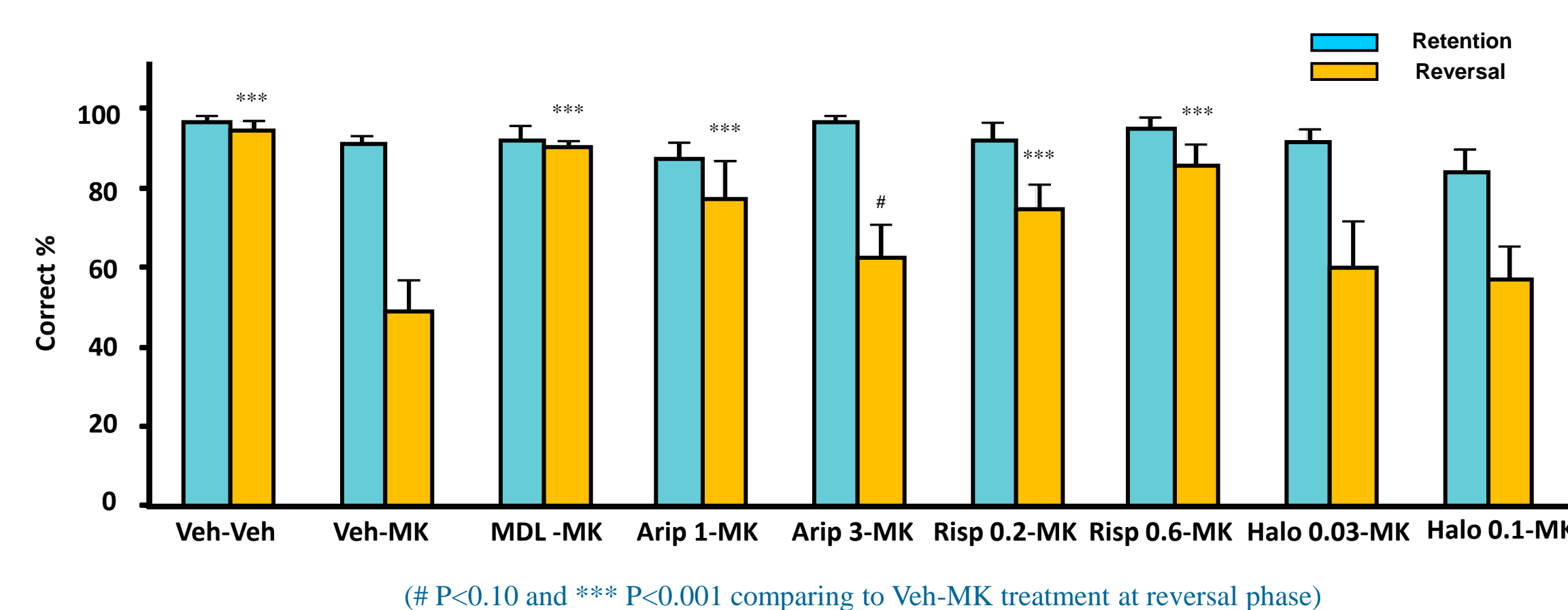
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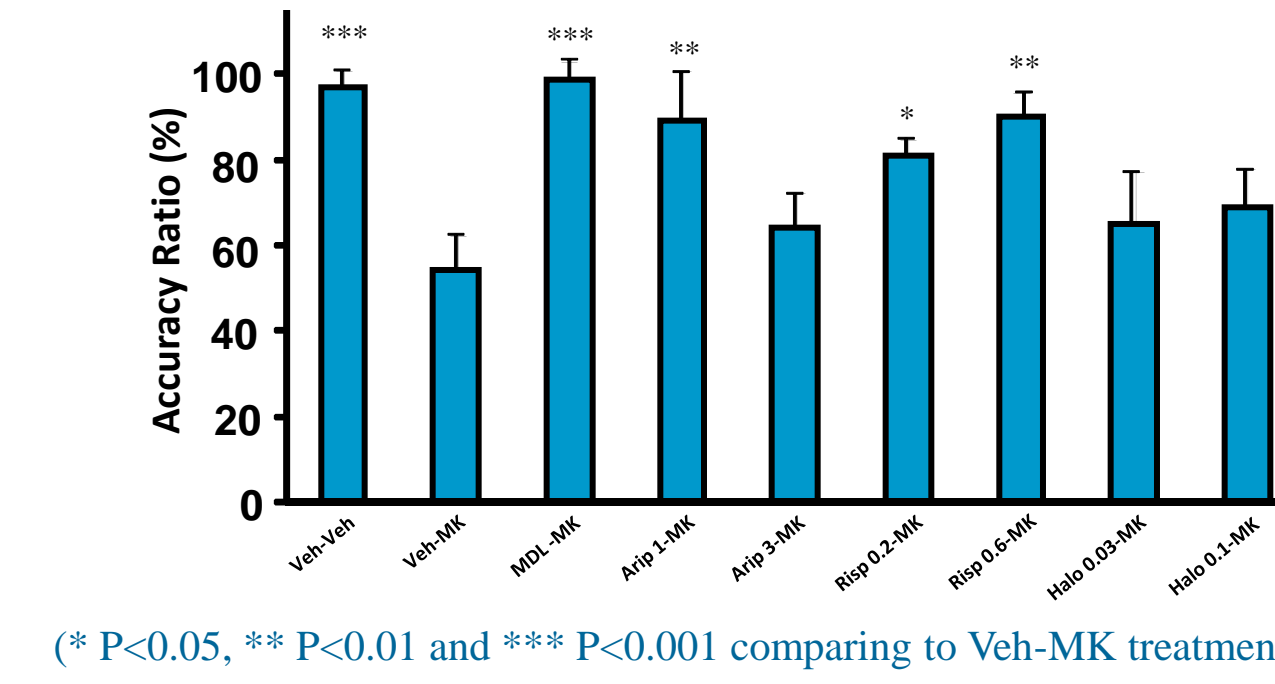
3. Typical vs. Atypical Antipsychotics

❖ In this Study, we compared atypical antipsychotics aripiprazole (1 and 3 mg/kg) and risperidone (0.2 and 0.6 mg/kg) with typical antipsychotic haloperidol (0.03 and 0.1 mg/kg) in MK-801 model with SRL test. Aripiprazole and risperidone (as well as positive control compound MDL 100907) showed efficacies in saving MK-801-induced deficits of behavioral flexibility. But haloperidol showed negative results.

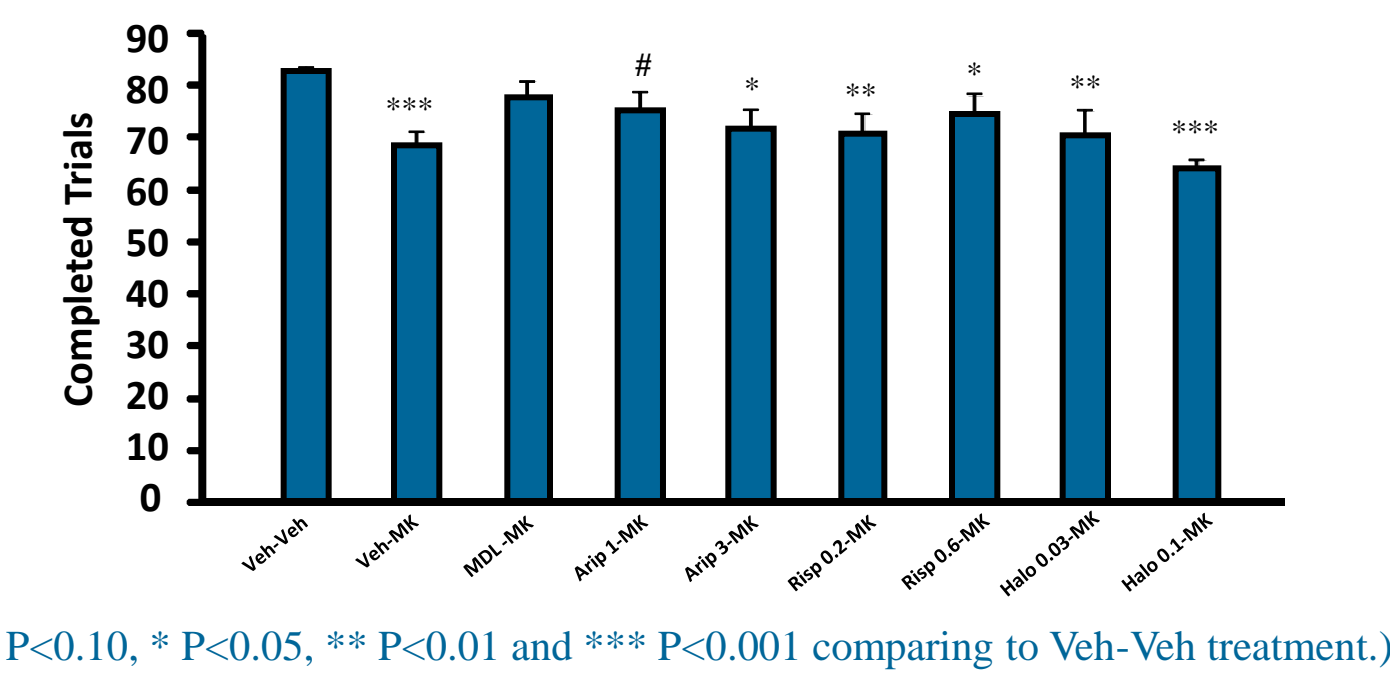
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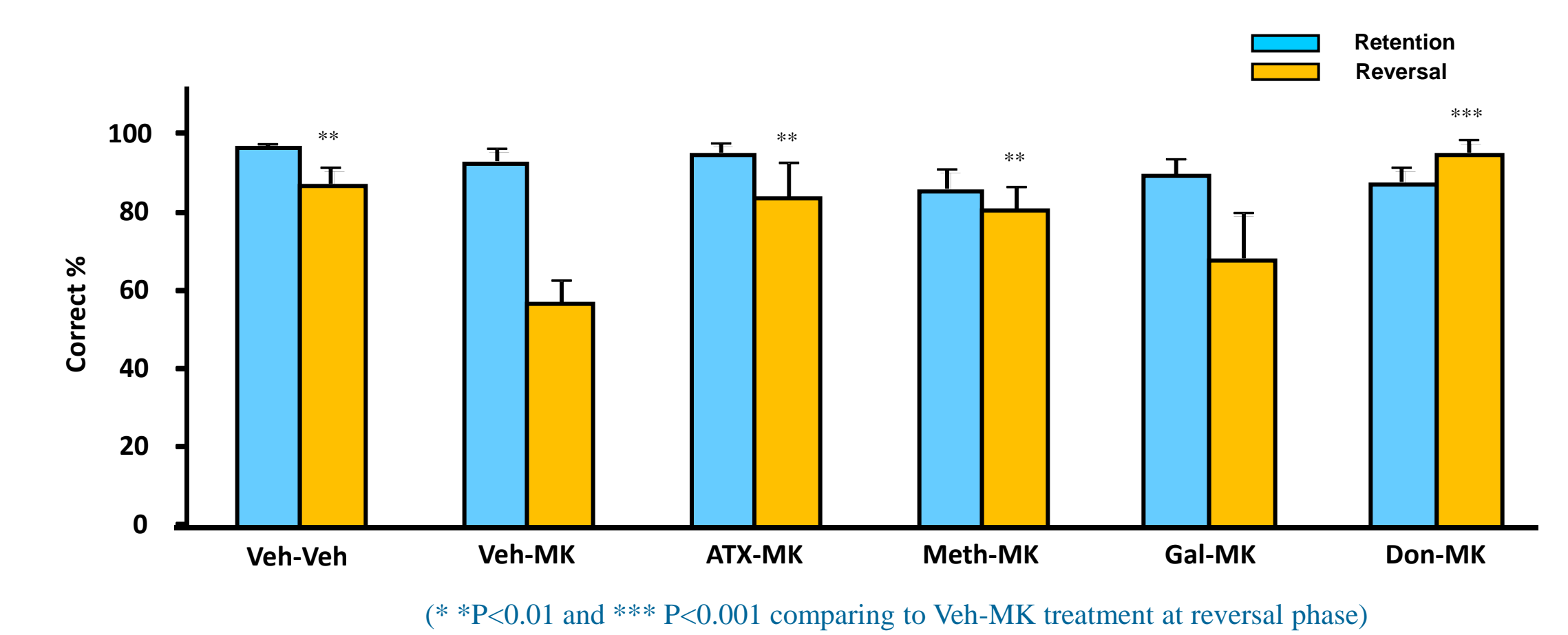
Completed Trials



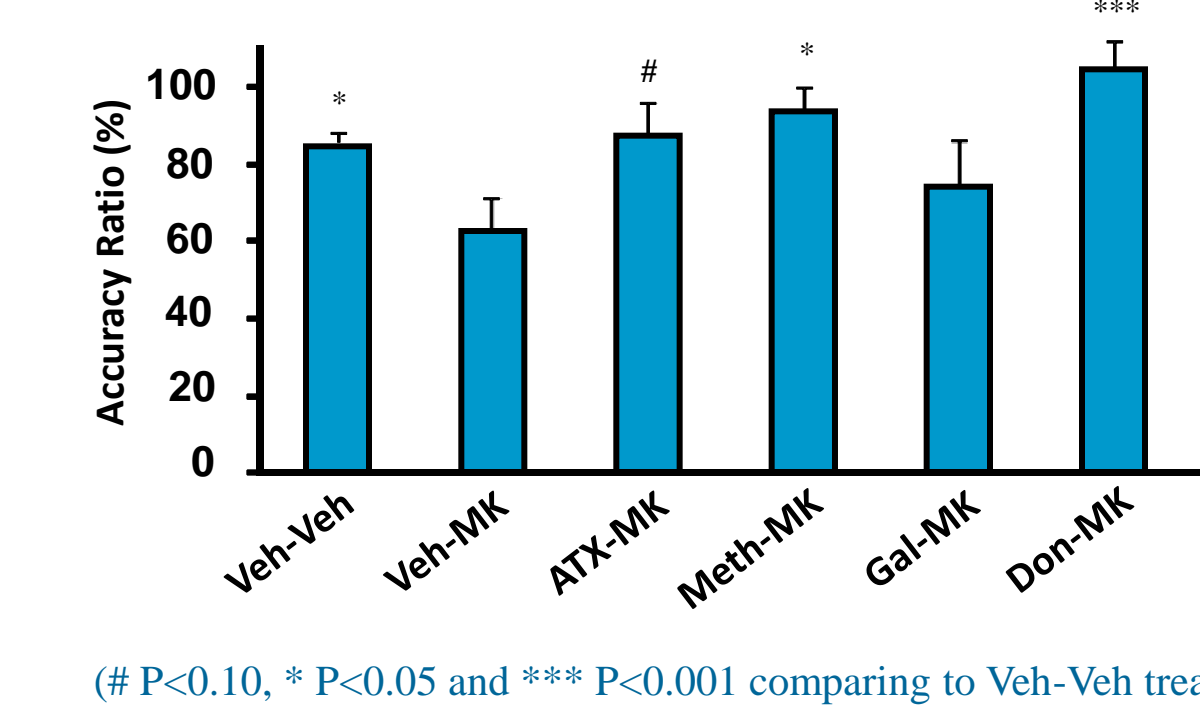
4. Effects of Non-antipsychotics

❖ We further tested four non-antipsychotics' effects in this model. Atomoxetine (1 mg/kg) and methylphenidate (4 mg/kg), two drugs to treat ADHD significantly reversed MK-801-induced cognitive flexibility deficits. For the two acetylcholine agonists galantamine (1 mg/kg) and donepezil (4 mg/kg), which are used to treat memory deficits in the early stage of Alzheimer's disease, only donepezil showed positive results.

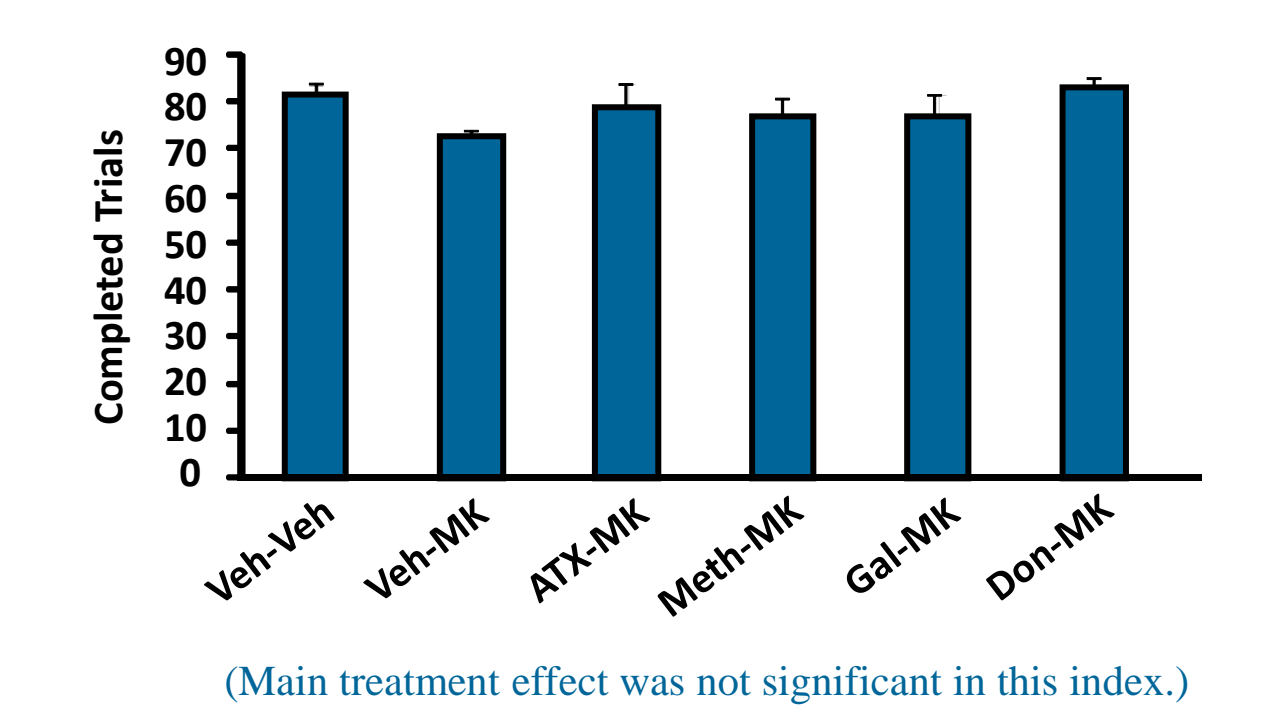
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Completed Trials



Summary

- MK-801 0.15 mg/kg significantly disrupted behavioral flexibility in serial reversal learning (SRL) test, indicating the face validity of this model in rats;
- Atypical antipsychotics olanzapine, clozapine, aripiprazole and risperidone, but not typical antipsychotic haloperidol, significantly saved behavioral flexibility in reversal learning when co-administrated with MK-801;
- Probably due to their anti-impulsive mechanisms, atomoxetine and methylphenidate also significantly reversed MK-801 induced deficits in serial reversal learning test;
- Acetylcholine agonist donepezil ameliorated MK-801-induced disruption of cognitive flexibility. This result may owe to its memory enhancement effects.