

# Modulation of impulsivity and attentional performance in high and low attentive rats by methylphenidate and atomoxetine in the 5 choice serial reaction time task

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## Background

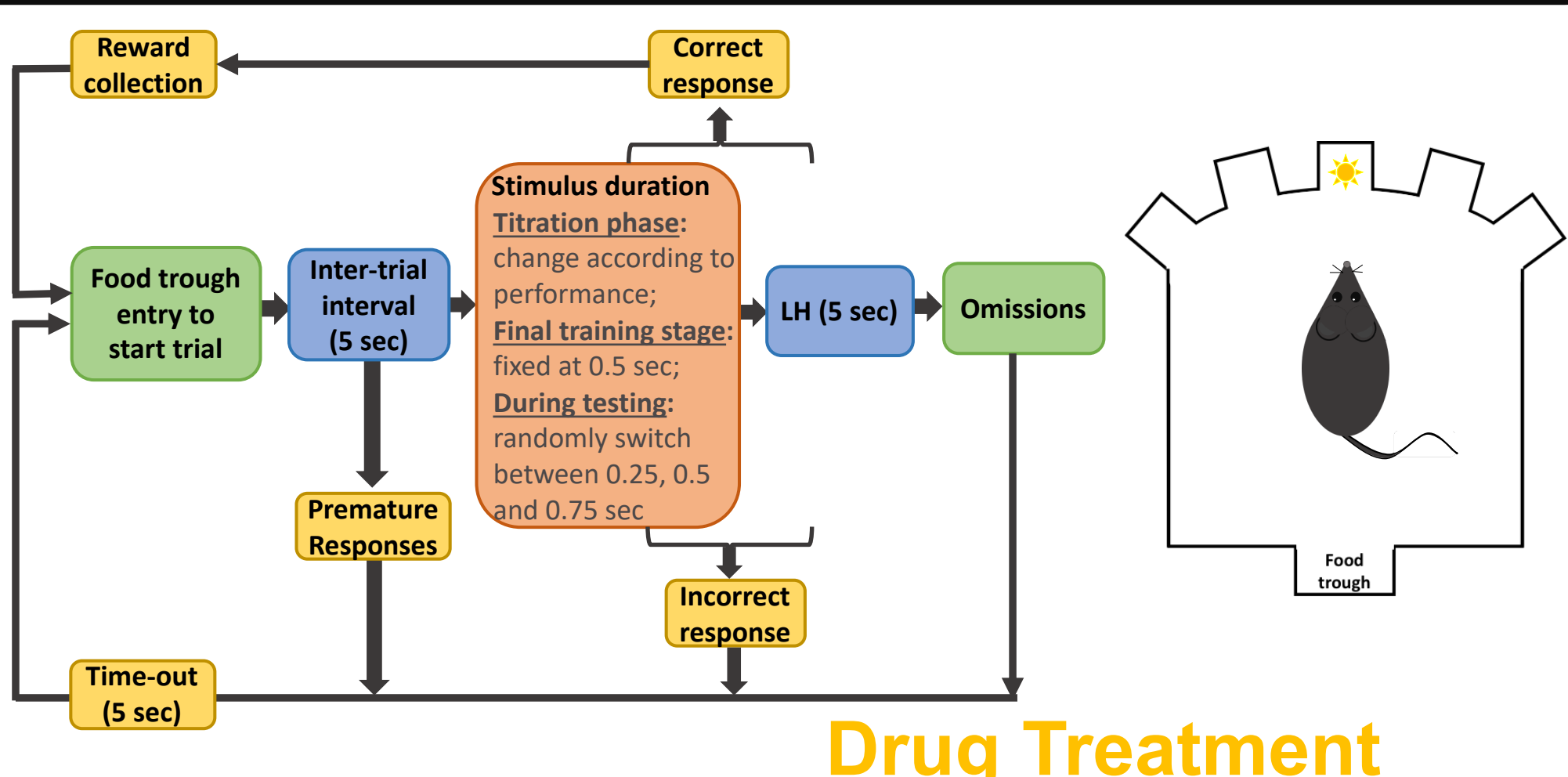
- Attention deficit/hyperactivity disorder (ADHD) is characterised by core symptoms of inattention and/or high impulsivity.
- These core symptoms enable ADHD to be subclassified into three different subtypes: inattentive, hyperactive-impulsive and combination type.
- Attention and impulsivity can be measured in rodents using the 5-choice serial reaction time task (5-CSRTT), an analogue to human continuous performance task.
- Reducing stimulus duration (SD) in the 5-CSRTT increases attention demand of the task and helps detect the improvement of attention by pharmacological manipulations.
- Current treatments for ADHD include methylphenidate (dopamine transporter (DAT) and noradrenaline transporter (NAT) inhibitor) and atomoxetine (NAT inhibitor).
- Methylphenidate and atomoxetine were shown to increase and decrease impulsivity in the 5-CSRTT respectively, with differential effects seen in attention measures.

**Aim: to assess effects of methylphenidate and atomoxetine on attention in high (HA) and low attentive (LA) animals using the 5-CSRTT with variable SD.**

## Methods

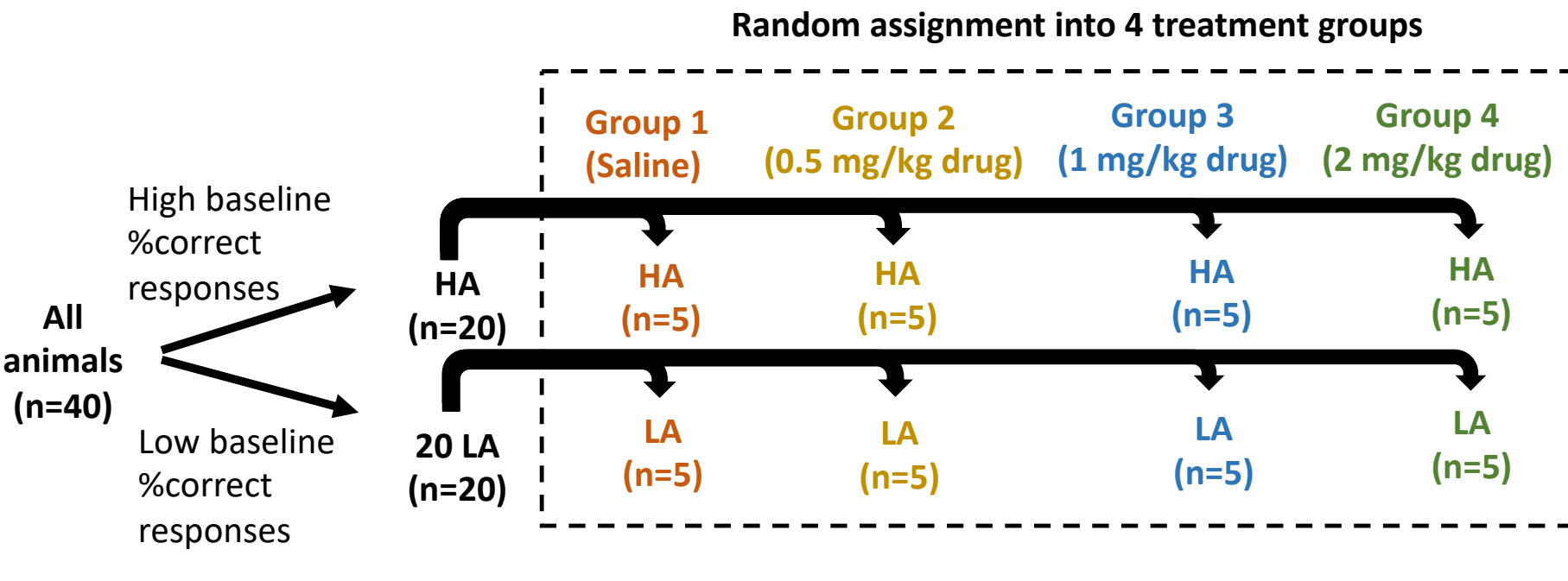
### 5-CSRTT Training

- A titration method was used to facilitate the 5-CSRTT training. SD was decreased after a correct response or increased after an omission/ incorrect response.
- After animal performance stabilised in the titration phase, animals were trained in the final stage (SD fixed at 0.5 sec) until their performance was stable for at least 5 sessions.



### Drug Treatment

- Animals were separated into HA and LA subgroups according to their mean % correct responses of the last 5 final-stage training sessions.
- The testing consisted of 4 treatment days, with each separated by a 1 week wash-out. Animals were randomly assigned into 4 treatment groups before each testing day to receive atomoxetine (first 2 days) or methylphenidate (last 2 days) (0.5, 1 and 2 mg/kg, i.p.).

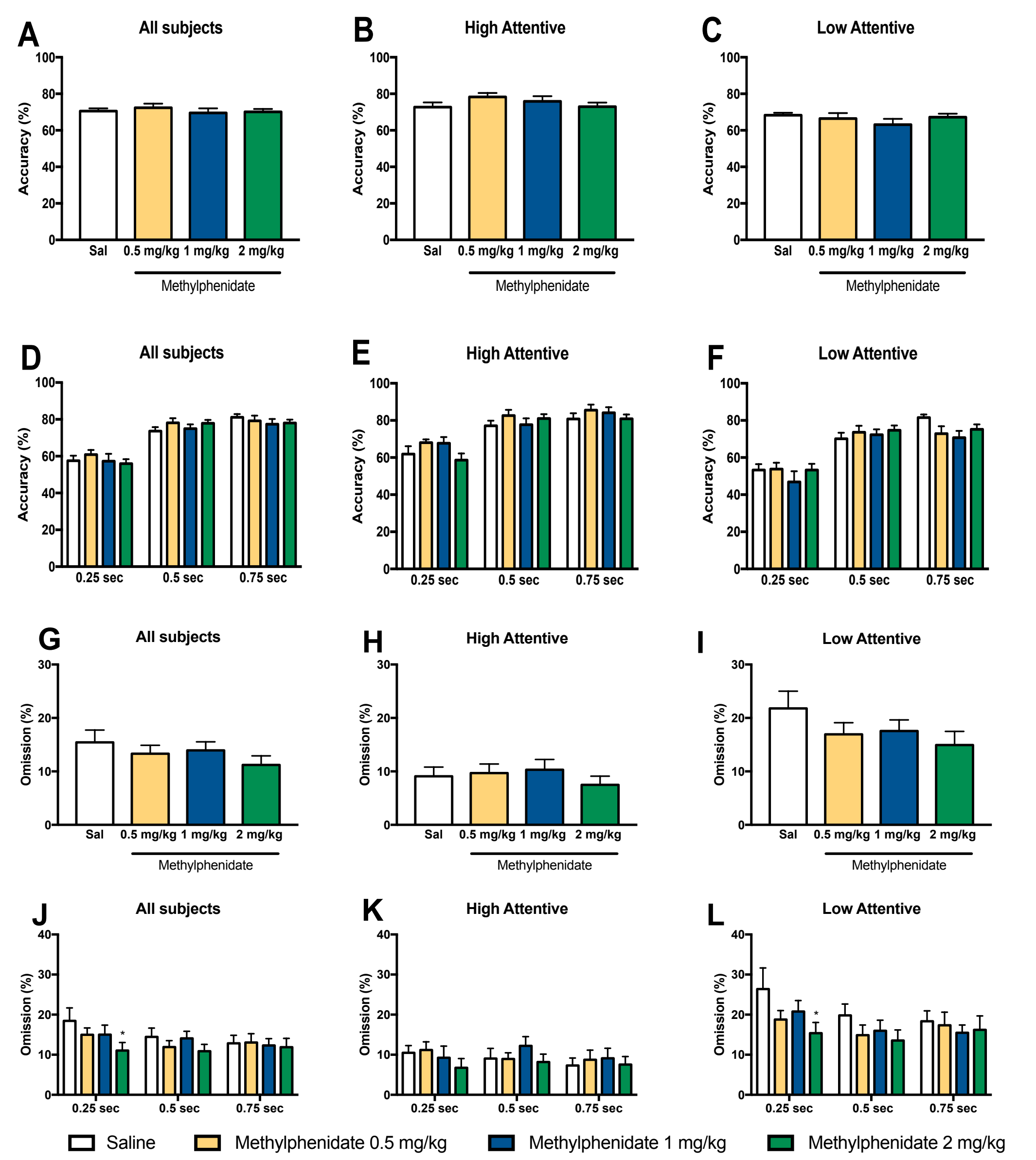


## Results: Attention

One-way and two-way ANOVA were used to analyse drug effects on the accuracy/omissions averaged across all SDs (A-C, G-I) and within each SD (D-F, J-L) respectively, followed by Dunnett's post-hoc test (\*p<0.05, \*\*p<0.01, \*\*\*p<0.001, \*\*\*\*p<0.0001). All data are presented as mean ± SEM.

### Methylphenidate improved attention

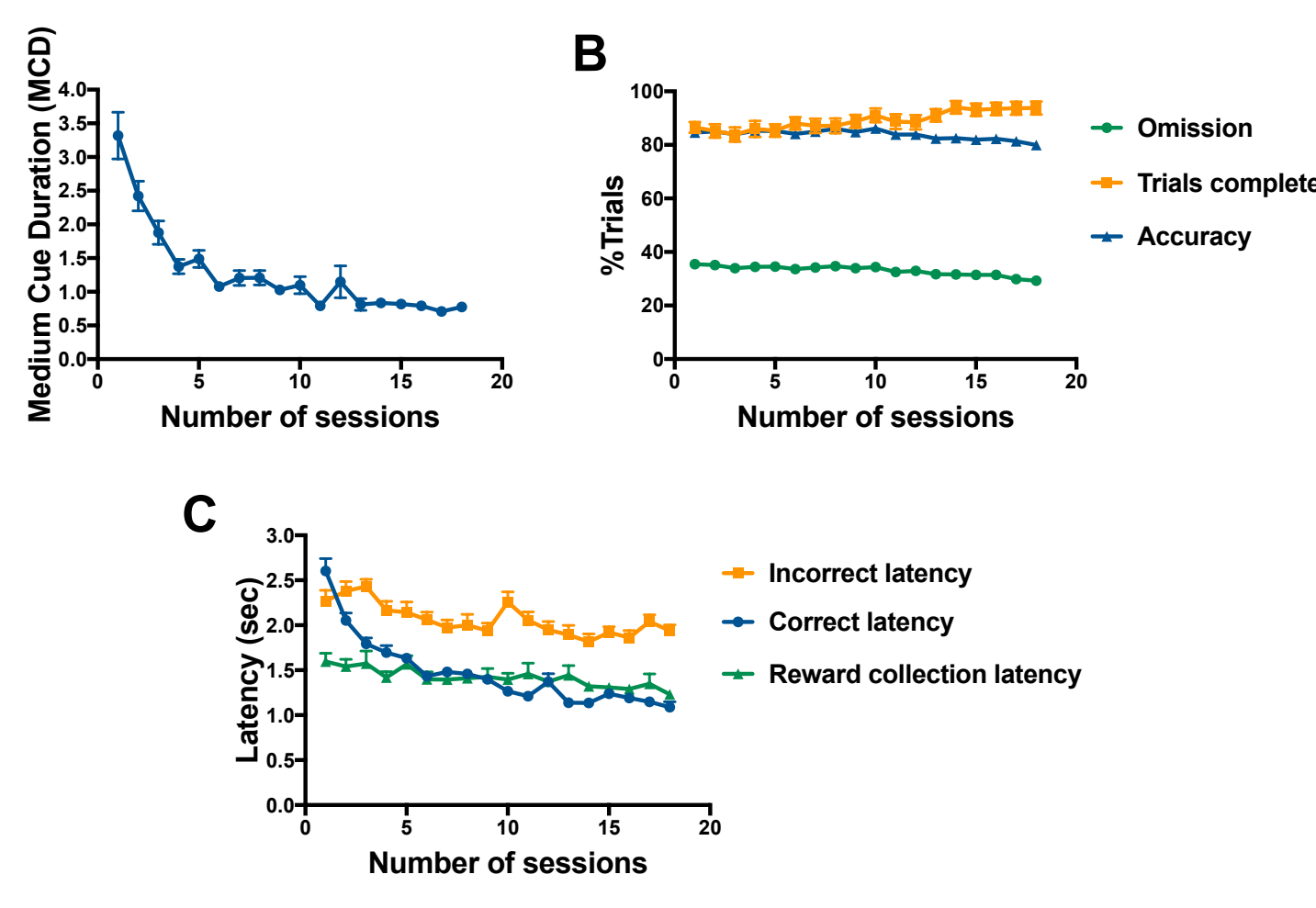
- No significant effects of methylphenidate were observed in accuracy.
- Methylphenidate (2 mg/kg) significantly decreased omissions in LA animals at 0.25 sec SD, suggesting improved attention.
- Methylphenidate did not influence the number of trials competed, percentage correct/incorrect responses, perseverative responses or response latencies.



## Results: Training

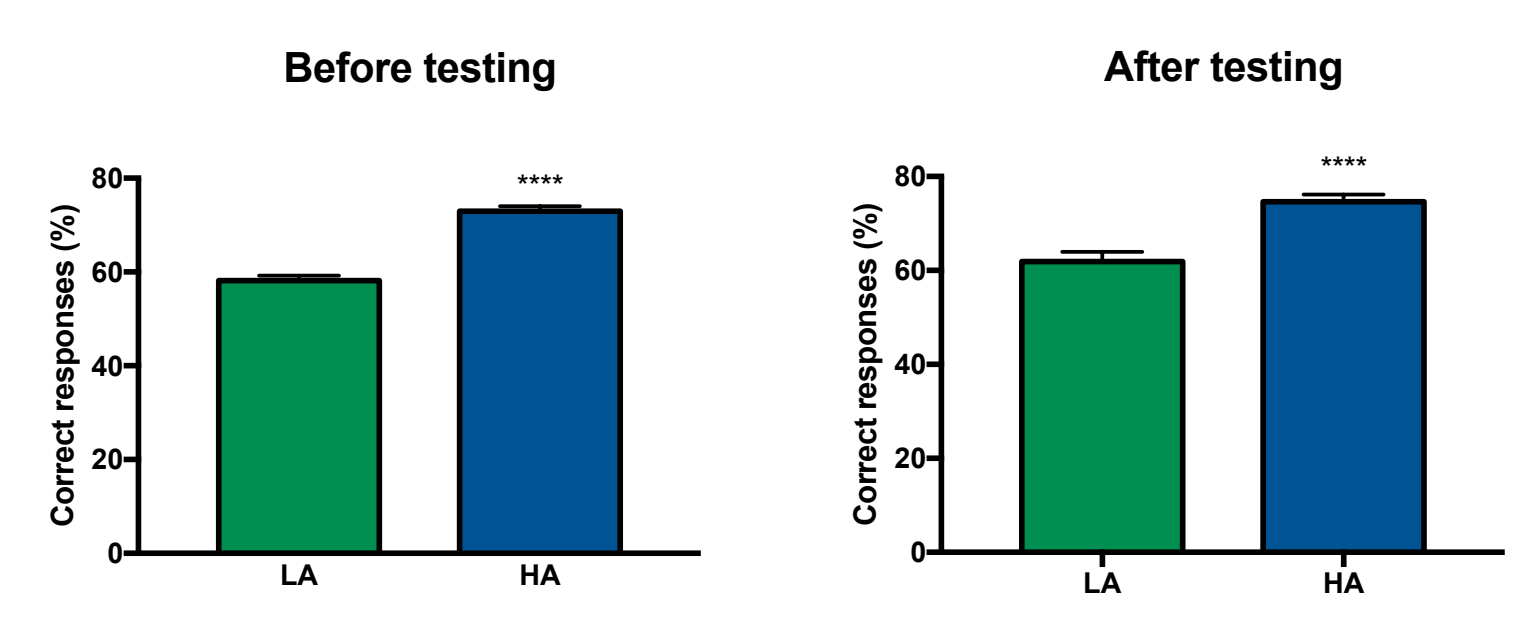
### Animal performance quickly stabilised during training

- Measures of the median cue duration (MCD, the medium value of the SD within each session excluding the first 15 trials) (A), attention (B) and response speed (C) quickly stabilised during the first 18 sessions.
- All 40 animals achieved a stable performance in the titration phase after 33.93 ± 0.80 (mean ± SEM) sessions, with MCD of 0.5 ± 0.02 sec.
- All 40 animals reached stable performance at 0.5 sec SD after 11 ± 1.03 more sessions.



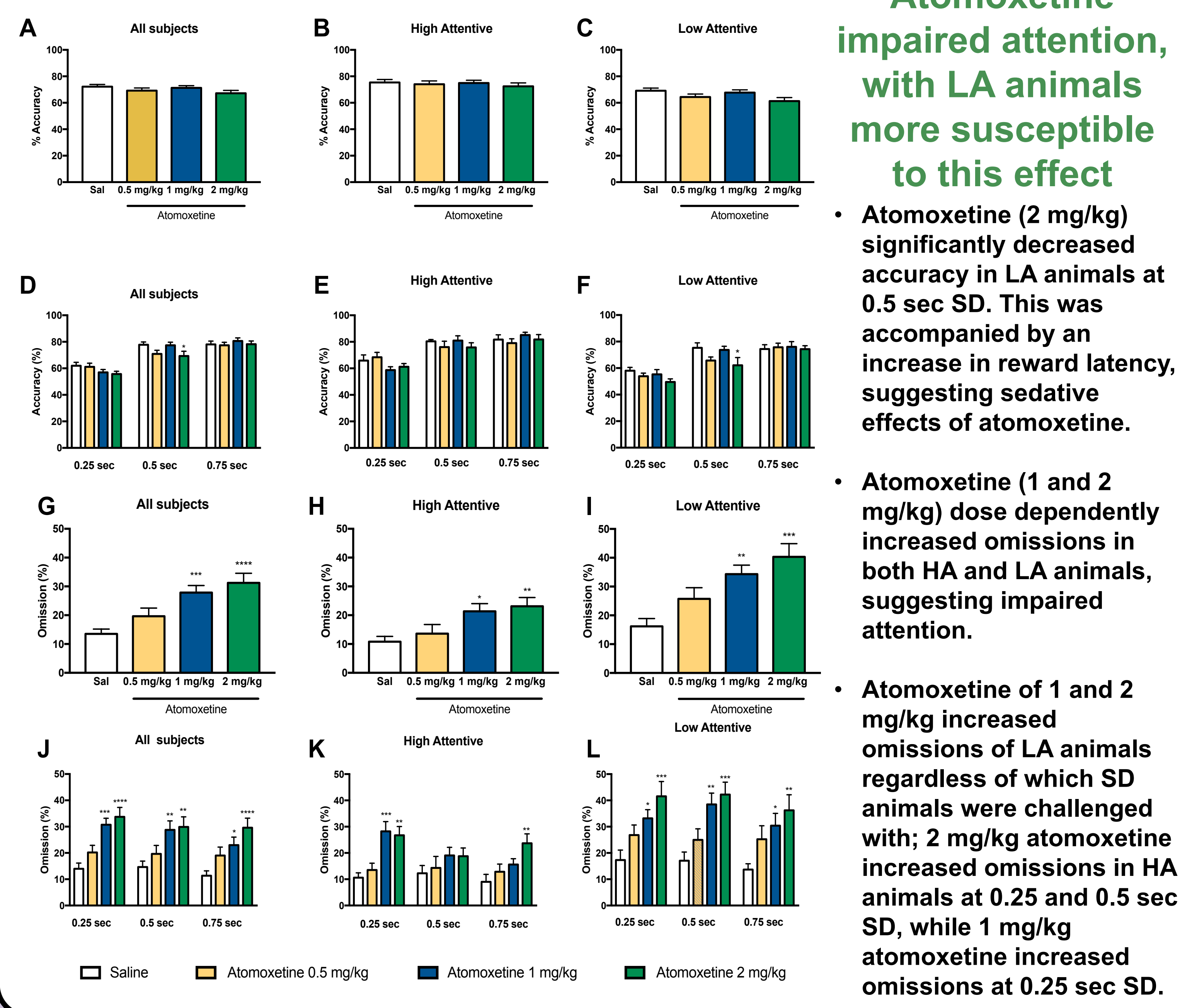
### Animal performance remained stable during the experiment

- %correct responses of the HA groups was significantly different from that of the LA group both before and after drug testing (two-tailed t-test, \*\*\*\*p<0.0001; data are presented as mean ± SEM).



### Atomoxetine impaired attention, with LA animals more susceptible to this effect

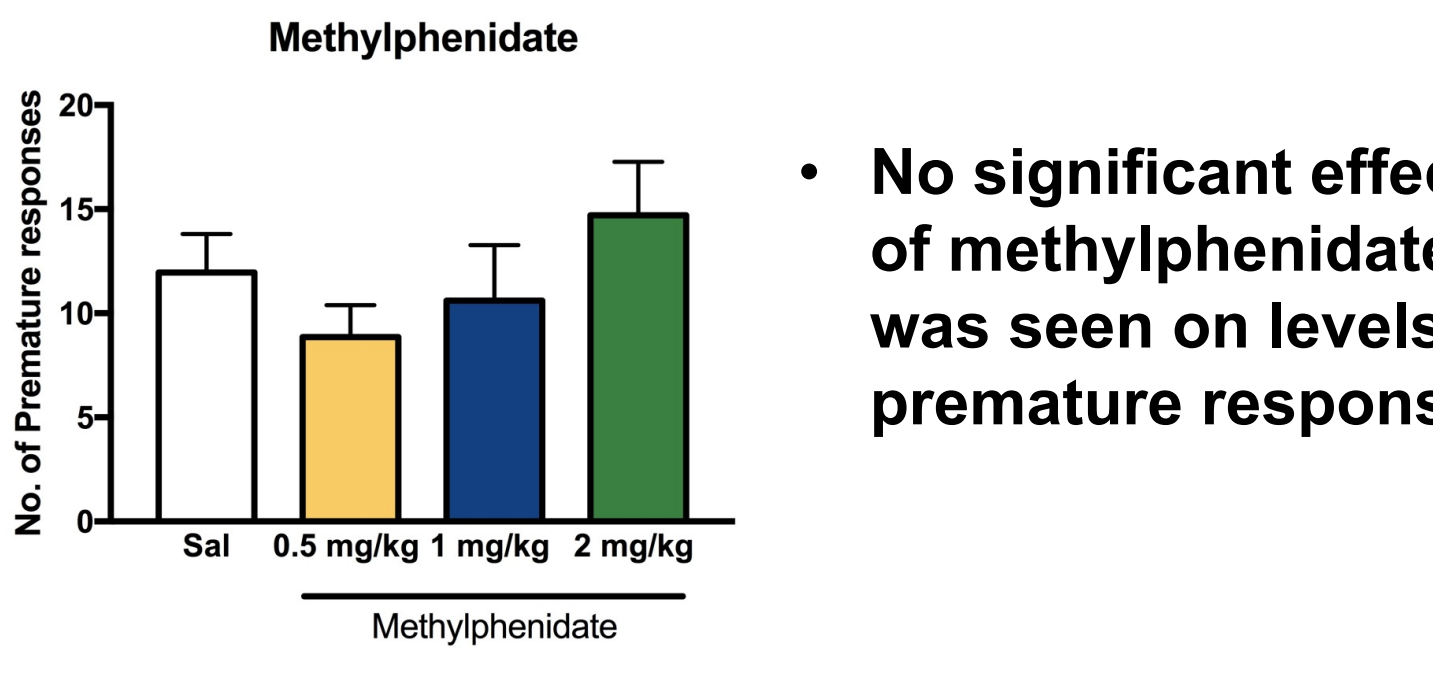
- Atomoxetine (2 mg/kg) significantly decreased accuracy in LA animals at 0.5 sec SD. This was accompanied by an increase in reward latency, suggesting sedative effects of atomoxetine.
- Atomoxetine (1 and 2 mg/kg) dose dependently increased omissions in both HA and LA animals, suggesting impaired attention.
- Atomoxetine of 1 and 2 mg/kg increased omissions of LA animals regardless of which SD animals were challenged with; 2 mg/kg atomoxetine increased omissions in HA animals at 0.25 and 0.5 sec SD, while 1 mg/kg atomoxetine increased omissions at 0.25 sec SD.



## Results: Impulsivity

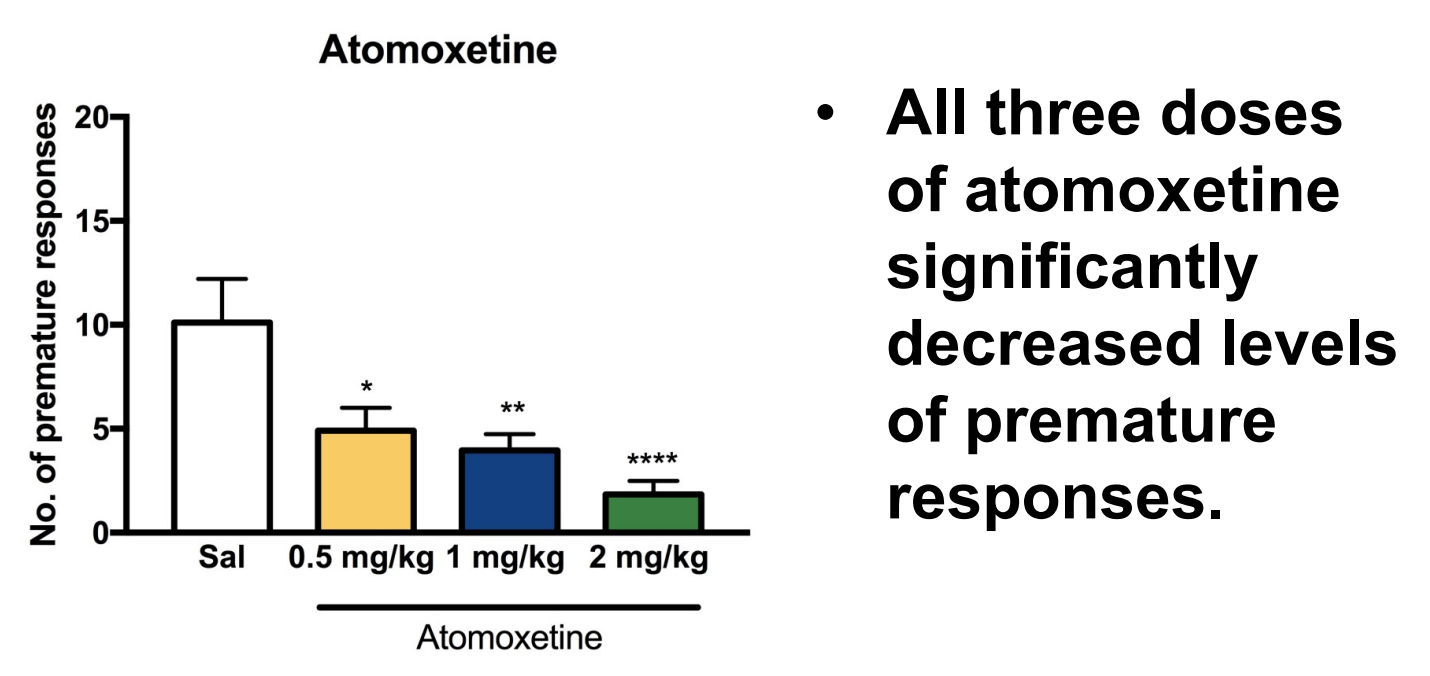
Data were analysed using one-way ANOVA, followed by Dunnett's post-hoc test (\*p<0.05, \*\*p<0.01, \*\*\*p<0.001, \*\*\*\*p<0.0001). All data are shown as an average of all SDs and are presented as mean ± SEM.

### Methylphenidate did not affect impulsivity



- No significant effects of methylphenidate was seen on levels of premature responses.

### Atomoxetine decreased impulsivity



- All three doses of atomoxetine significantly decreased levels of premature responses.

## Discussions

- Methylphenidate did not affect impulsivity but improved attention in LA animals; atomoxetine was effective in decreasing impulsivity while worsening attention in all animals.
- Differential effects of atomoxetine and methylphenidate may result from distinct mechanisms of actions of these two drugs in prefrontal cortex, nucleus accumbens and striatum.
- Dual inhibition of NAT and DAT may be a better target for improving attention, while NAT inhibitors may be more effective in decreasing impulsivity.
- This provides great insights in personalizing treatment for different ADHD subtypes and development of improved pharmacotherapies in the future.

## References

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