CHARACTERIZATION OF THE EFFECTS OF α4ß2* nACh RECEPTOR PARTIAL AGONIST CYTISINE IN THE TWO-CHOICE SERIAL REACTION TIME TASK

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INTRODUCTION

• It has been suggested that nicotine has attention-enhancing properties and attenuates response inhibition. Nicotine was found to improve target detection and to decrease reaction time, but also to impair the ability to withhold premature responses (i.e. to increase impulsivity).

•These effects of nicotine are thought to be mediated by α4β2*, α4β4* and α3β2* nicotinic acetylcholine receptor (nAChR) subtypes (Blondel A. et al. (2000) Psychopharmacology, 149: 293-305).

AIM

The purpose of this study was to investigate effects of cytisine, a partial agonist of α4β2* nAChR, on the performance in the two-choice serial reaction time task (2-CSRTT).

MATERIALS AND METHODS

❑ Animals

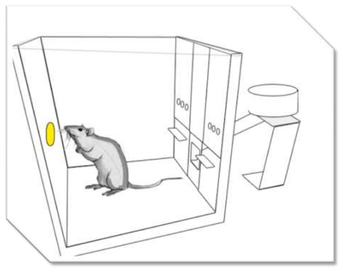
• 10 adult male Wistar rats (Rappolovo, St.Petersburg) were housed individually with restricted access to food (14-16 g of standard lab chow/day/rat)

❑ Apparatus

• standard operant conditioning chambers
• the front panel of the chamber contained two levers separated with a pellet magazine
• 3 light bulbs (yellow, red, green) upon each lever
• illuminated hole on the back panel of the chamber for trial initiation

❑ Experimental procedure

• acquisition criteria - >70% correct responses, between 40-60% left hand side preference, <10% omissions
• session duration – 30 min or until 100 trials completed
• experiments were held 6 days/week

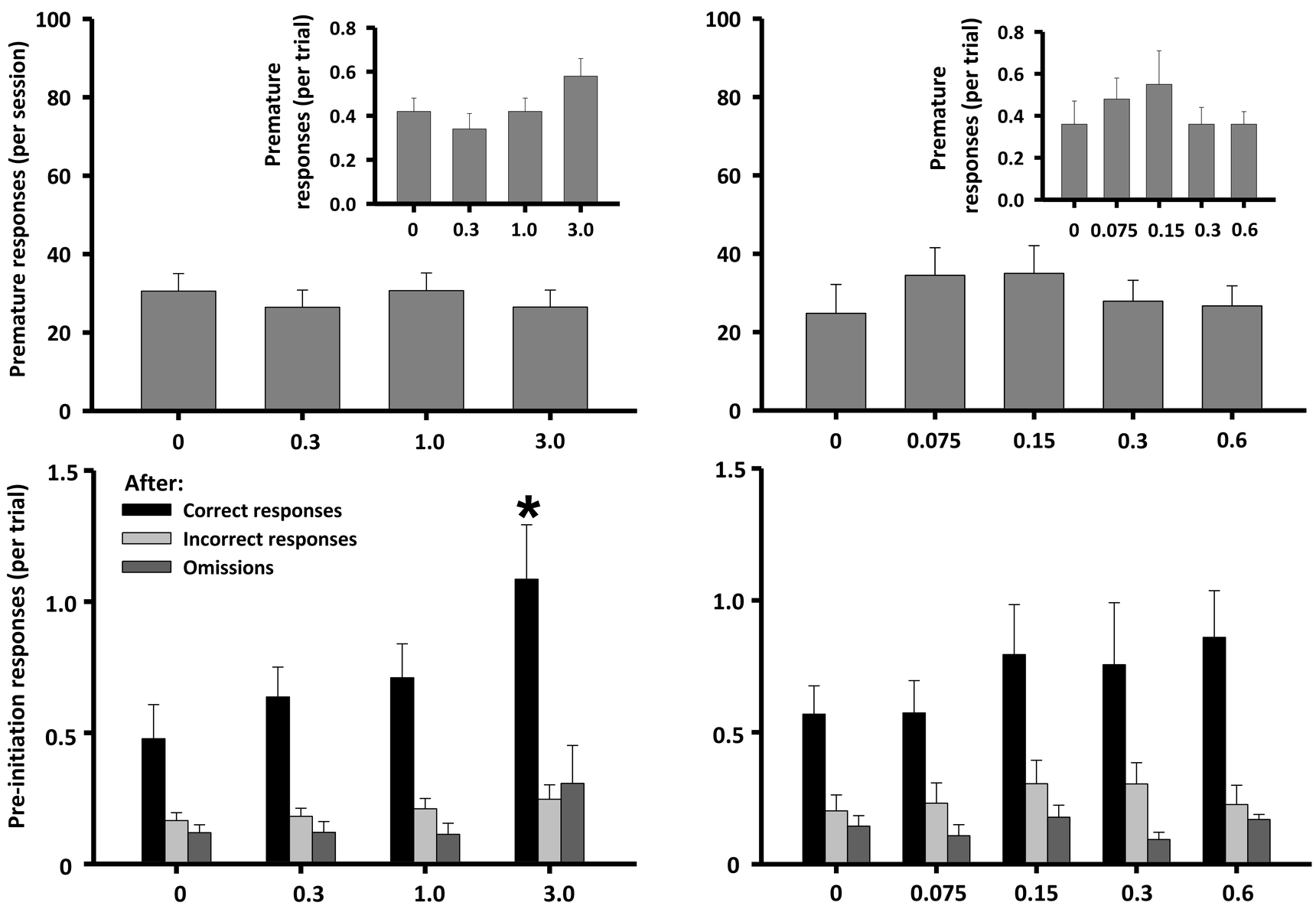


• Trials were initiated with nose-poking into the illuminated hole
• Responses during 5-s inter-trial interval (ITI) - *premature responses* - were punished with a 5-s *time-out*

• Pressing on the lever highlighted with three colored bulbs (correct responses) during the *1-s stimulus presentation* or the *2-s limited hold* ended with delivery of a food pellet
• Continued lever pressing after a correct response before pellet collection *(perseverations)* and *pre-initiation lever responses* were recorded but had no programmed consequence

• *Incorrect responses*, *omissions* did not lead to the delivery of a food pellet and resulted in a *5-s time-out period*, during which the houselight was extinguished

EXPERIMENT A. *EFFECTS OF ACUTE CYTISINE AND NICOTINE ADMINISTRATION*



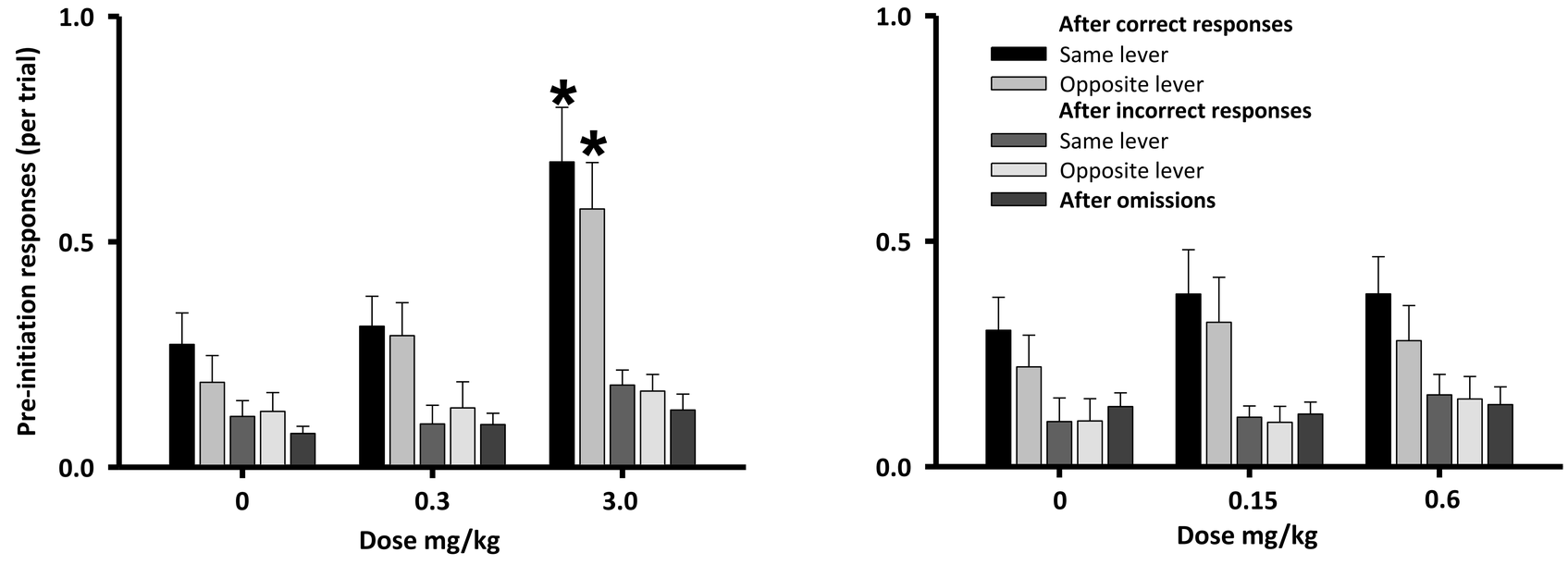
Effects of cytisine and nicotine on premature responses and on pre-initiation responses after acute cytisine and nicotine administration. Cytisine (0.3-3.0 mg/kg, s.c.) was injected 15 min prior to the test. Nicotine (0.075-0.6 mg/kg, s.c.) was injected 5 min prior to the test. Data represent mean ±S.E.M. * P < 0.05 (Dunnett's test) compared to vehicle control treatment. N=10 for each data point.

Task measures	Cytisine				Nicotine				
	Vehicle	0.3 mg/kg	1.0 mg/kg	3.0 mg/kg	Vehicle	0.075 mg/kg	0.15 mg/kg	0.3 mg/kg	0.6 mg/kg
Accuracy (%)	81.1 ± 2.6	84.7 ± 1.8	83.7 ± 1.7	79.3 ± 2.6	85.6 ± 2.1	83.9 ± 3.3	82.7 ± 2.0	85.7 ± 2.4	86.0 ± 2.7
Trials completed	74.5 ± 6.7	81.0 ± 4.8	74.0 ± 4.5	55.8 ± 2.2 *	72.6 ± 4.2	77.8 ± 5.5	71.3 ± 4.7	80.8 ± 5.1	74.6 ± 4.4
Omissions	6.1 ± 1.6	6.1 ± 0.9	4.3 ± 0.8	4.2 ± 1.2	5.7 ± 1.0	5.8 ± 1.4	5.3 ± 0.8	3.9 ± 1.1	5.5 ± 0.9
Perseverations	1.8 ± 0.7	3.7 ± 1.5	3.3 ± 1.7	2.7 ± 1.3	4.3 ± 2.0	2.1 ± 0.7	2.7 ± 1.6	2.5 ± 1.1	2.9 ± 1.2
Response latency (s)	0.8 ± 0.1	0.8 ± 0.03	0.8 ± 0.1	0.8 ± 0.1	0.8 ± 0.1	0.8 ± 0.1	0.8 ± 0.1	0.8 ± 0.1	0.7 ± 0.1
Latency to reward retrieval (s)	0.5 ± 0.03	0.5 ± 0.05	0.5 ± 0.03	0.5 ± 0.03	0.5 ± 0.04	0.5 ± 0.03	0.6 ± 0.1	0.5 ± 0.04	0.5 ± 0.04
Side preference (%)	58.6 ± 1.9	54.7 ± 1.4	53.1 ± 1.1	63.1 ± 2.5	55.7 ± 1.9	56.4 ± 1.8	57.2 ± 1.2	55.9 ± 2.1	54.7 ± 0.7

Effects of cytisine and nicotine on other task measures. Data represent mean ±S.E.M. * P < 0.05 (Dunnett's test) compared to vehicle control treatment. N=10 for each data point.

EXPERIMENT B. *EFFECTS OF CYTISINE AND NICOTINE ON PRE–INITIATION RESPONDING*

In order to clarify the nature of *pre-initiation responses*, they were analyzed as responses *on the same/opposite lever* regarding previous type of response (*correct, incorrect, omission*).



Effects of cytisine and nicotine on pre-initiation responses after administration of selected doses of cytisine (left) and nicotine (right). Data represent mean ±S.E.M. * P < 0.05 (Dunnett's test) compared to vehicle control treatment. N=10 for each data point.

CONCLUSIONS

• Neither cytisine nor nicotine had any reliable effects on percent of correct responses (accuracy) and number of premature and perseverative responses.
• Administration of the highest dose of cytisine (3.0 mg/kg) attenuated the number of completed trials due to significantly increased number of pre-initiation responses.
• Further analysis found that only number of pre-initiation responses on both levers performed after correct responses became persistently elevated following cytisine administration

In summary, the results of the present study demonstrate that cytisine induced performance disruption indicative of increased pre-initiation, but not premature responding. Such deficits might reflect an aspect of response disinhibition, other than loss of impulse control, that represents an additional measure of compulsivity related to cognitive inflexibility.

NO POTENTIAL CONFLICT OF INTERESTS