

Investigation into the beneficial effects of aerobic exercise on cognitive function in rodents.

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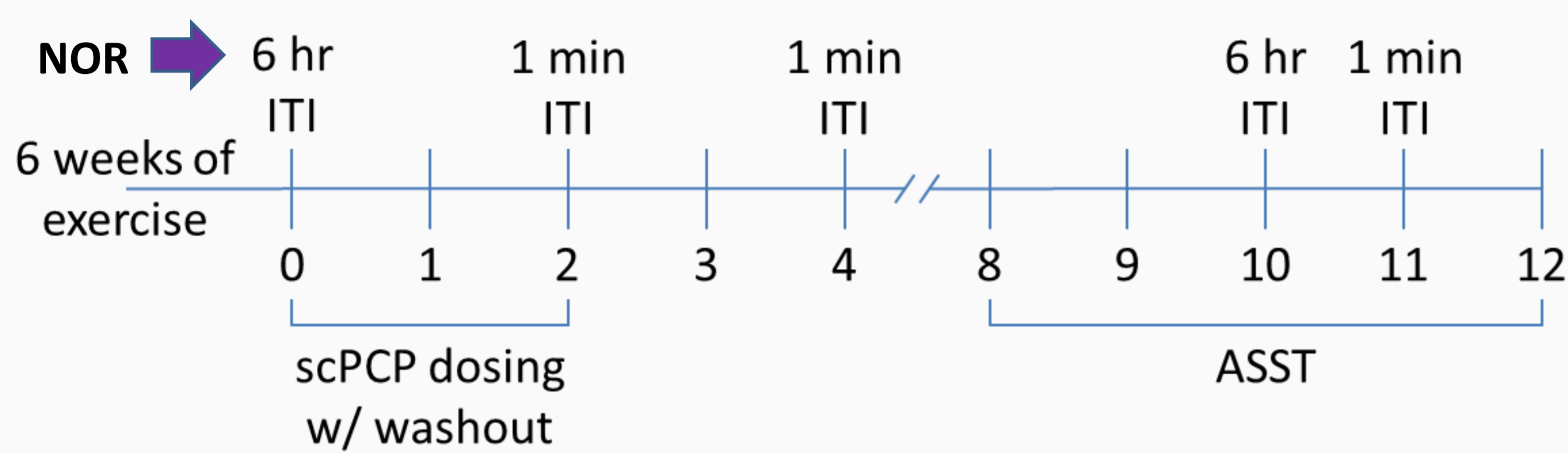


Introduction

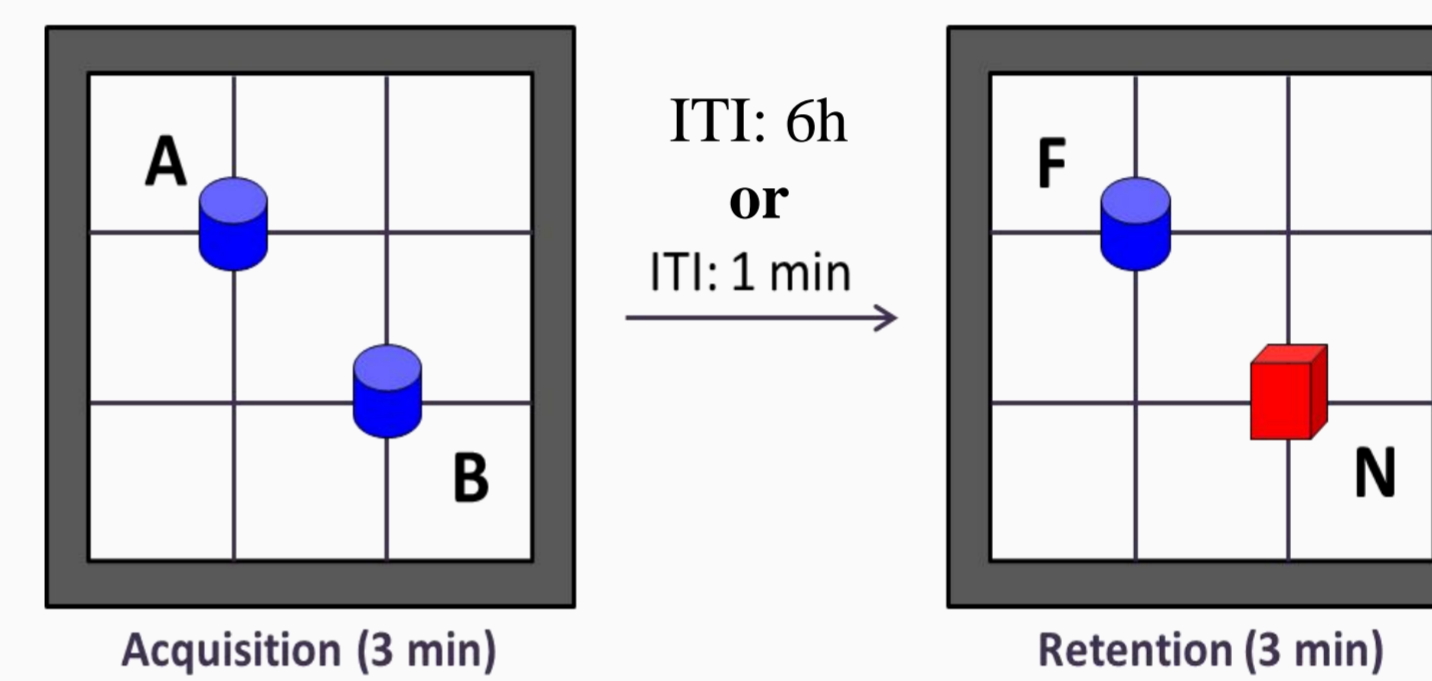
- Cognitive dysfunction is an unmet clinical need in several psychiatric and neurological disorders.
- No drug has yet received a licence for cognitive impairment associated with schizophrenia (Talpos et al, 2017).
- Aerobic exercise has been shown to improve cognitive deficits in schizophrenia patients (Falkai et al, 2017).
- We have previously demonstrated that exercise (1h/day, 5 days/week for 6 weeks) **reverses** a robust sub-chronic PCP-induced deficit in NOR which was sustained for 4- weeks. **Our aim** is to determine whether exercise will **prevent** the sub-chronic PCP- induced deficit.

The objective is to evaluate the effects of 6-weeks of wheel running on the 6h ITI NOR test and cognitive deficits induced by subsequent sub-chronic PCP treatment in the NOR and ASST tests.

Methods

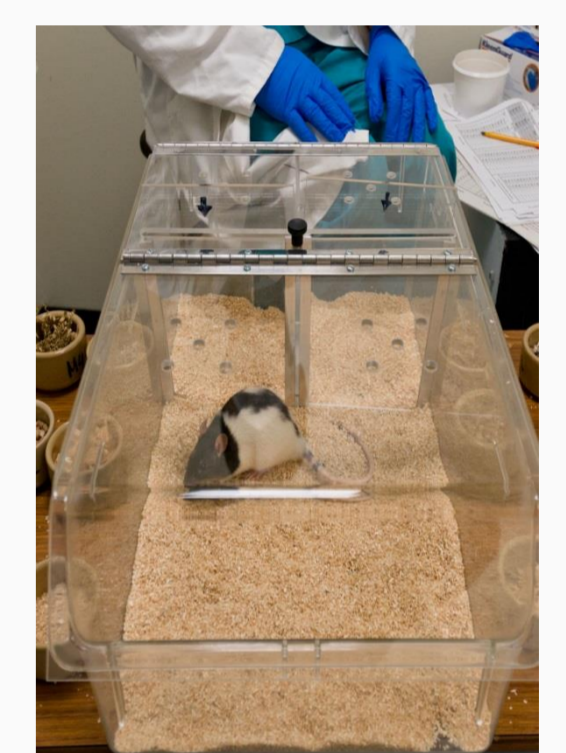


Novel object recognition (6h ITI or 1min ITI)



Attentional Set-shifting: ASST

Reasoning and problem solving
Rat analogue of the ID/ED test in CANTAB. Rewarded paradigm – 7 discriminations

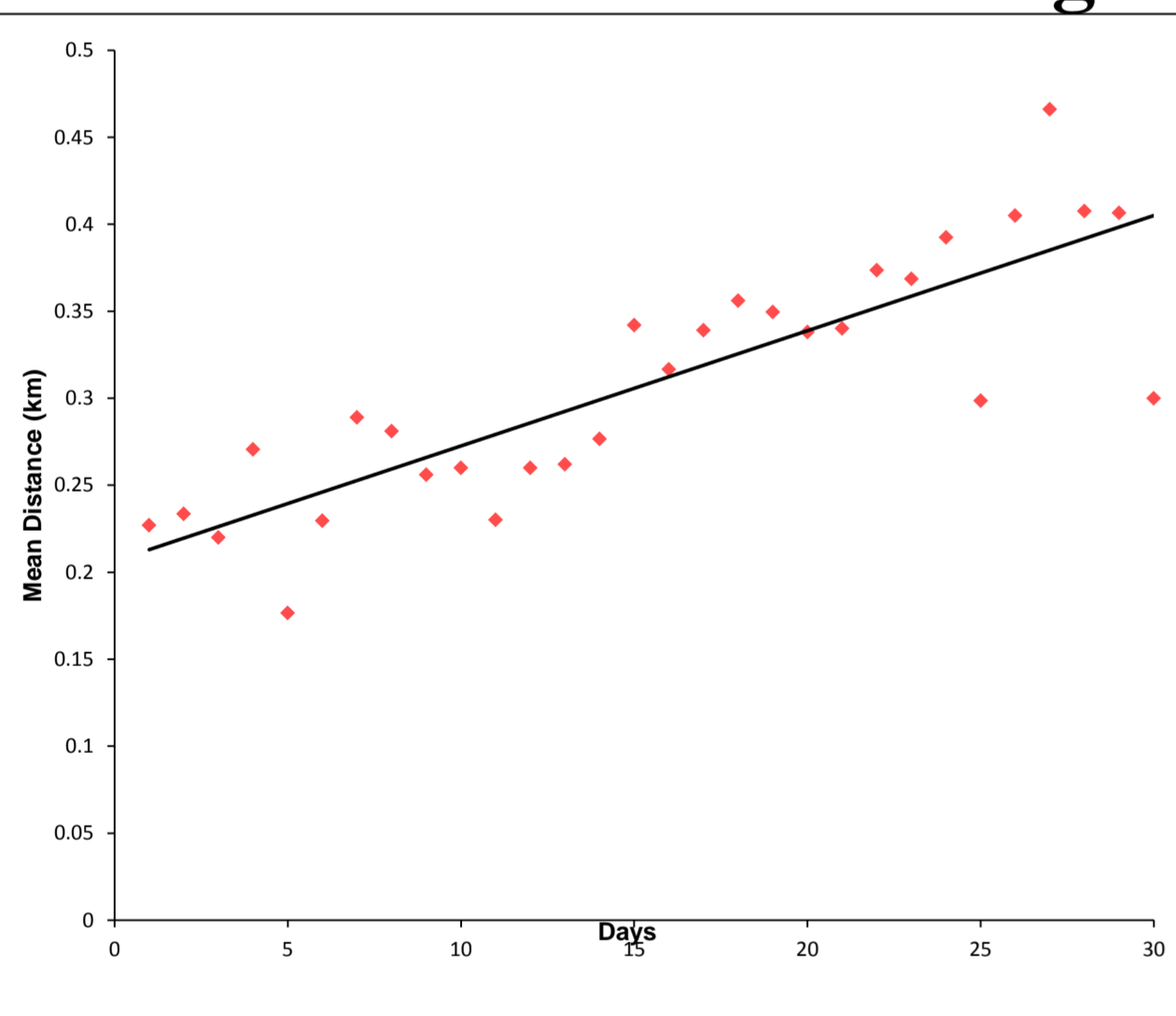


A total of 40 female Lister Hooded rats were divided into two groups (n=20 control and n= 20 exercised), they were given access to running wheels in individual cages for 1h/day, 5 days/week for 6 weeks. Rats were tested 48h and 10 weeks later in NOR using a 6h ITI.

Rats received sub-chronic phencyclidine (scPCP; 2 mg/kg) or vehicle i.p. twice daily for 7 days, followed by at least 7 days washout. Rats were tested in NOR using a 1min ITI, 2, 4, and 11 weeks post exercise. Rats were also tested for their cognitive performance in the ASST between 8-12 weeks post exercise regimen.

Results

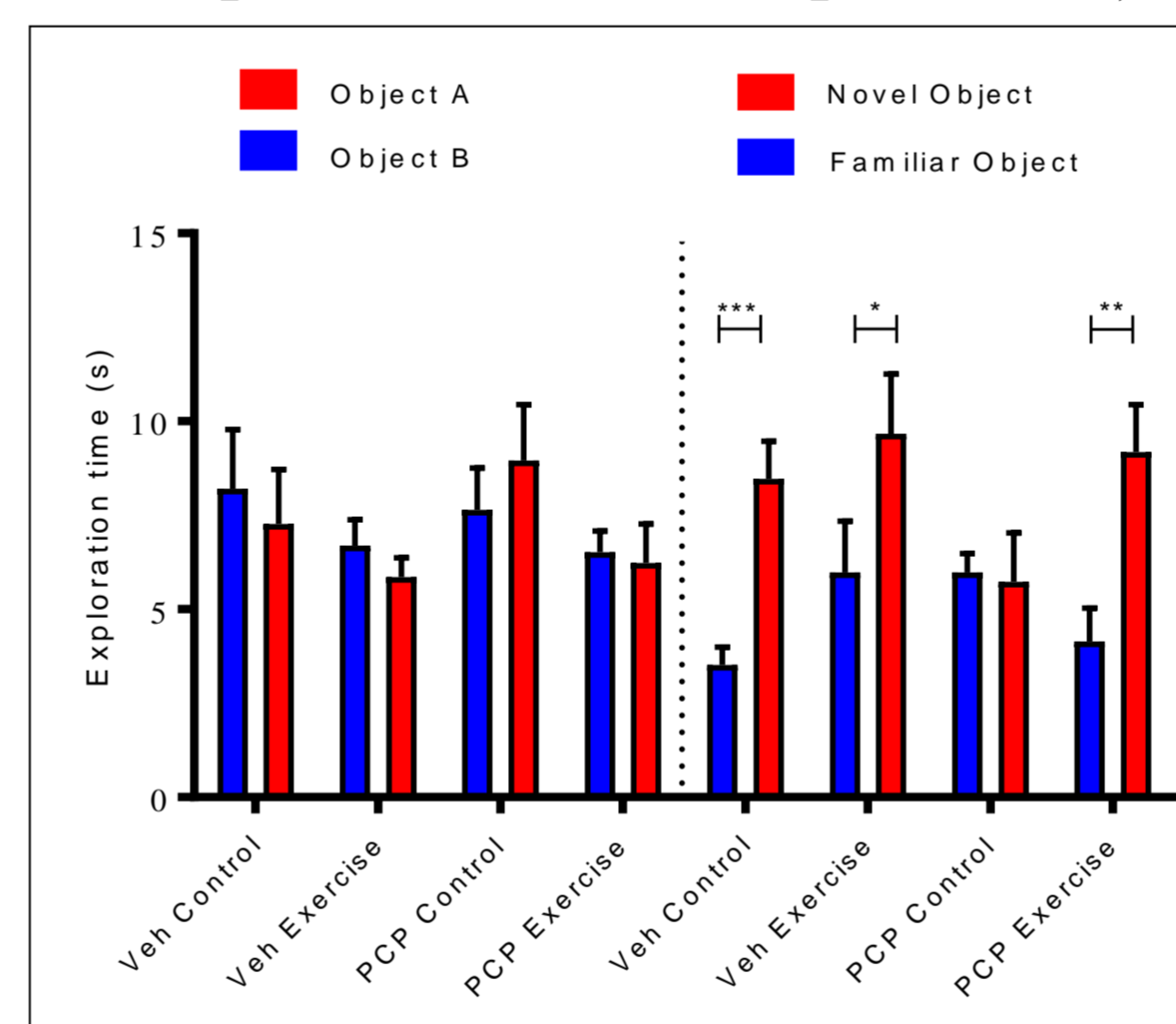
6-weeks Exercise Training



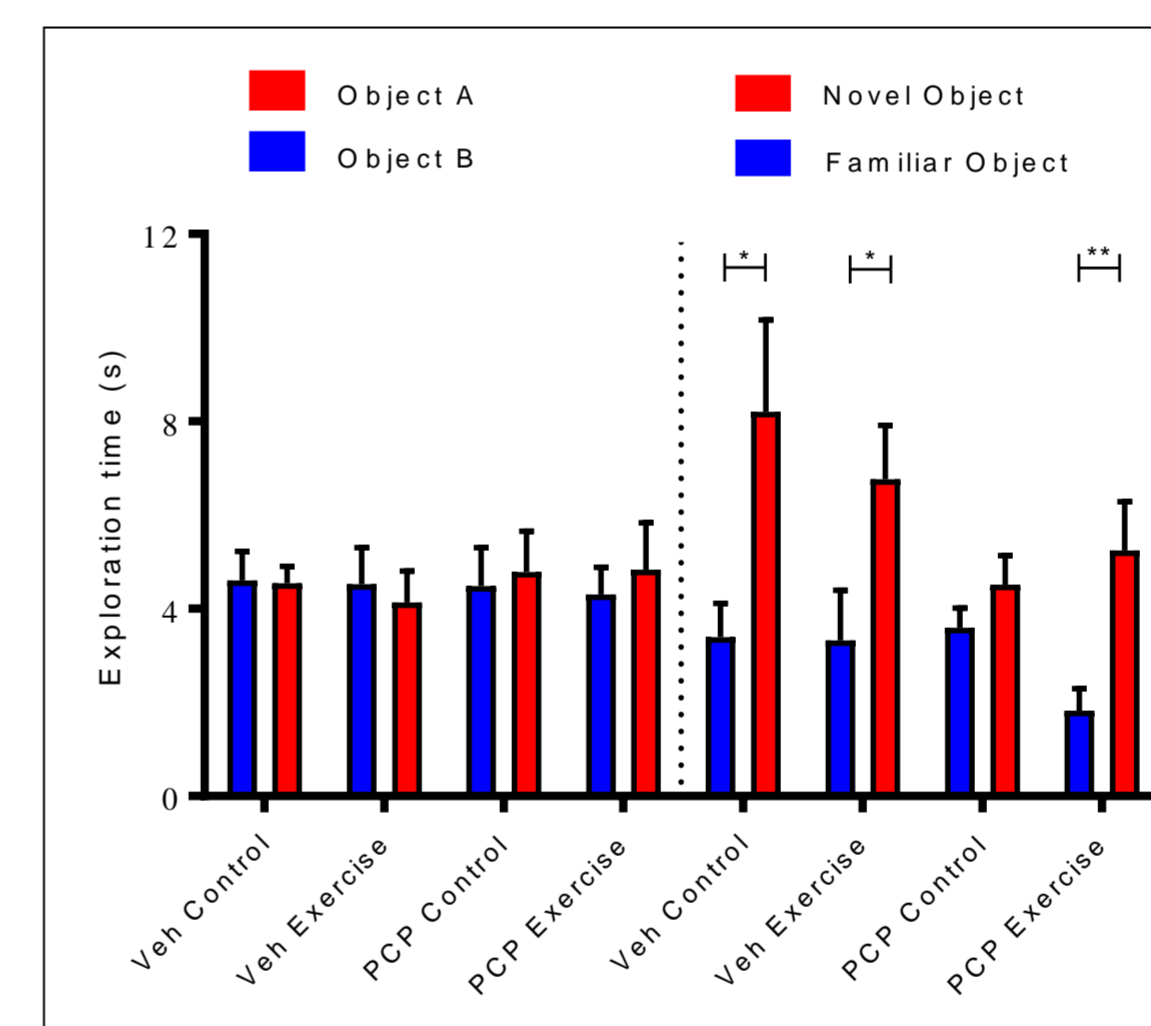
Significant increase in the mean running distance (km) during the exercise regimen (Linear regression analysis, $r=0.707$, $P<0.001$).

NOR: scPCP-induced deficit

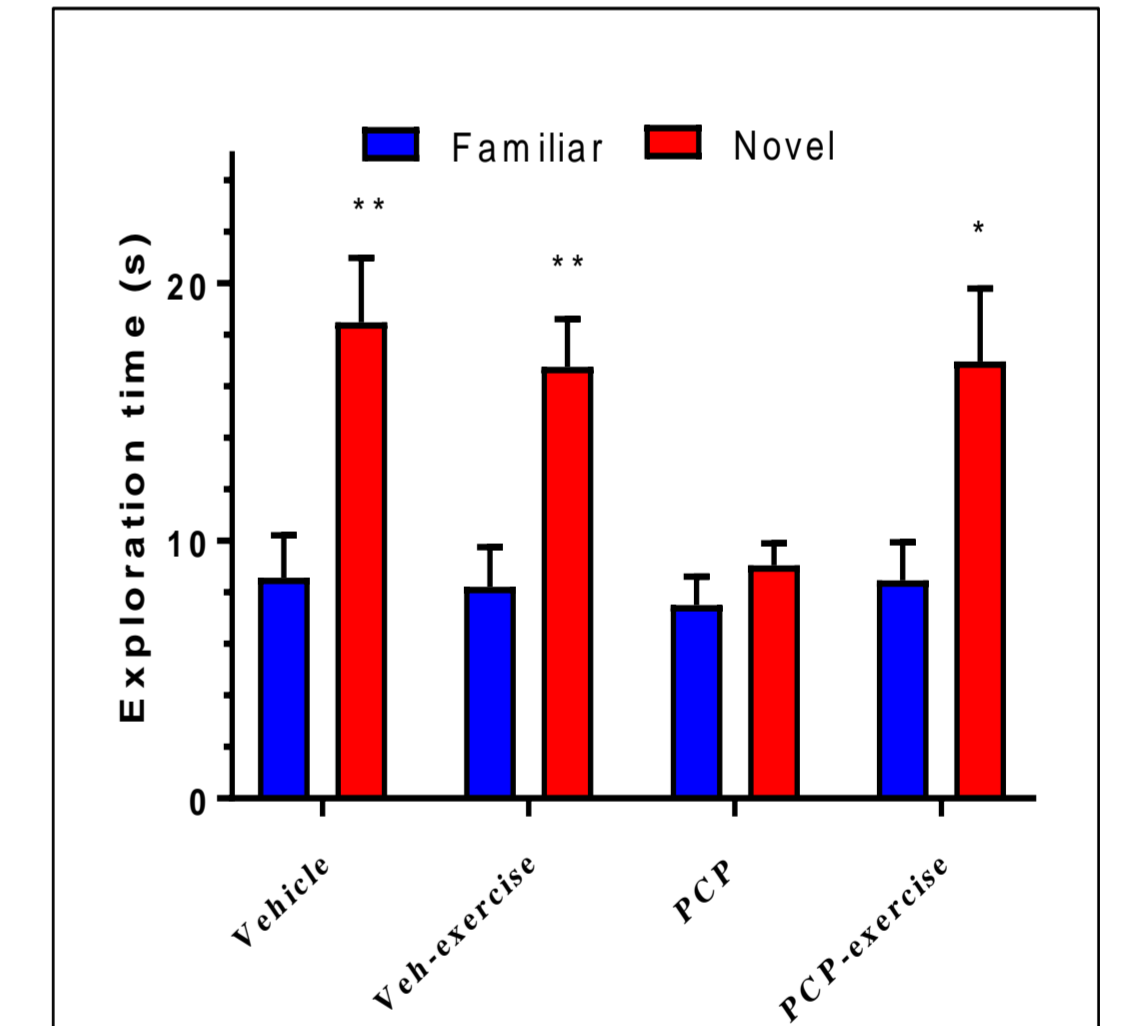
2 weeks post exercise (1-week post scPCP)



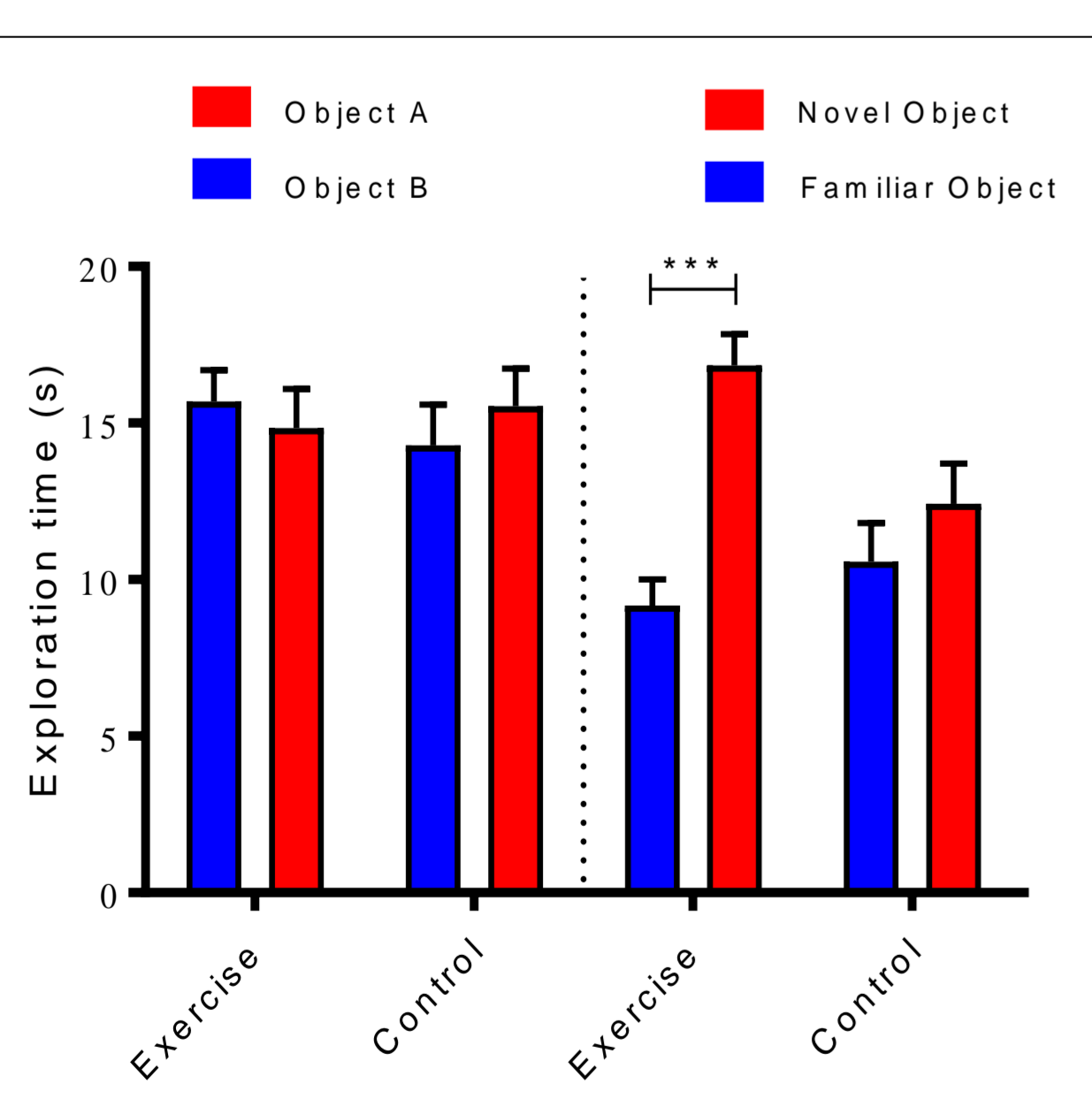
4 weeks post exercise (2-weeks post scPCP)



11 weeks post exercise (9-weeks post scPCP)

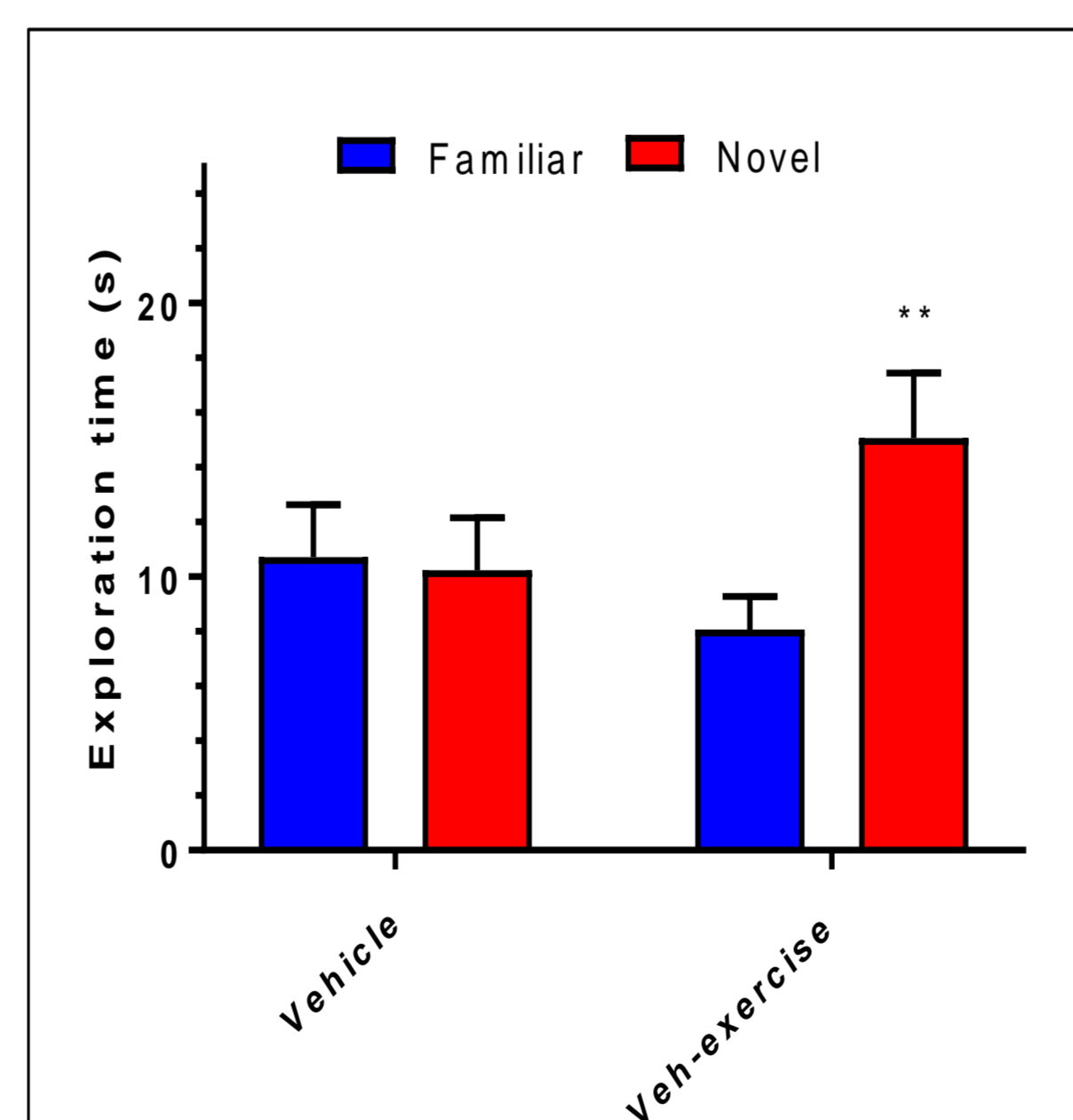


NOR: 6h ITI induced deficit 48h post exercise

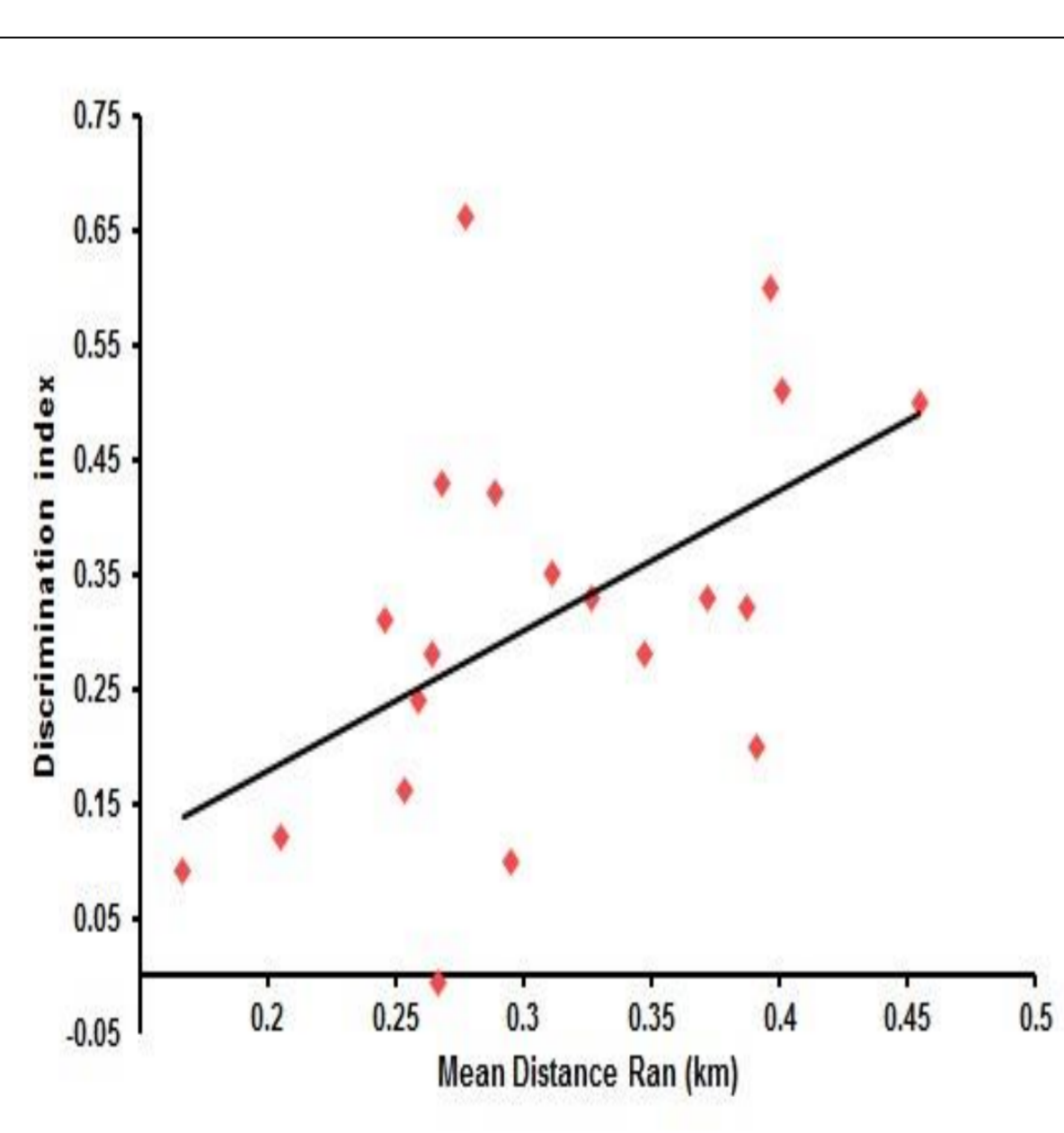


Exercise prevents the delay (6h ITI) dependent impairment in NOR 48h post exercise.

NOR: 6h ITI induced deficit 10 weeks post exercise



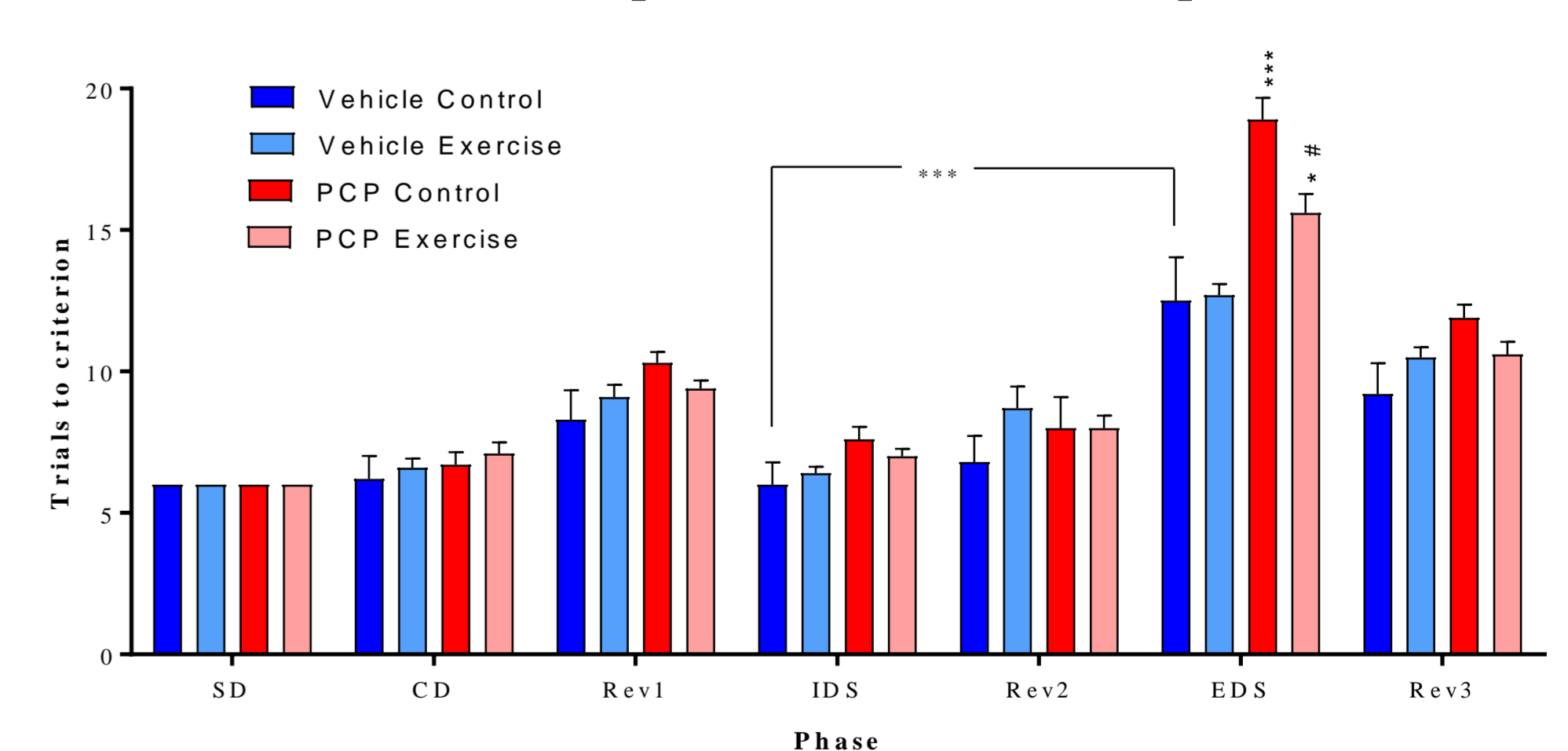
Exercise prevents the delay dependent impairment in NOR at 10 weeks post exercise



A positive correlation between the rats that ran furthest over the 6-weeks and the DI (Pearson's $r=0.514$, $P<0.05$).

- scPCP induces a reduction in the rats ability to discriminate between novel and familiar objects in non-exercised rats.
- Exercise prevents the scPCP-induced deficit (2-11 weeks post scPCP).

8-12 weeks post exercise (6-10 weeks post scPCP)



- scPCP induces an increase in the number of trials to criterion in the EDS phase of the ASST.
- Exercise prevents the scPCP induced ASST deficit 8-12 weeks post exercise.

Conclusions

- We show a positive relationship between the level of exercise and improved cognition in the 6h ITI NOR test.
 - This work demonstrates that aerobic exercise restores a delay-induced deficit in object recognition memory which is still effective 12 weeks post exercise.
 - Additionally we show that aerobic exercise produces a robust effect to prevent the scPCP-induced deficit in NOR up to 12 weeks post exercise.
 - The aerobic exercise regime also prevented the scPCP-induced deficit in ASST when tested between 8-12 weeks post exercise.
- Further work to evaluate the mechanisms of these powerful effects of aerobic exercise could inform future therapeutic strategies in patients with cognitive impairment.

References:

Falkai, P., Malchow, B. and Schmitt, A. (2017). Aerobic exercise and its effects on cognition in schizophrenia. *Current Opinion in Psychiatry*, 30(3), pp.171-175.
Talpos, J. (2017). Symptomatic thinking: the current state of Phase III and IV clinical trials for cognition in schizophrenia. *Drug Discovery Today*, 22(7), pp.1017-1026.