Brain-Derived Neurotrophic Factor and Exercise-Induced Reversal of Cognitive Deficit Symptoms of Relevance to Schizophrenia

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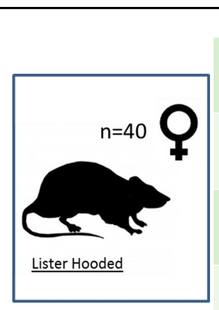
Introduction

Cognitive deficits in schizophrenia remain an unmet clinical need and have a significant impact on outcome and quality of life for patients and carers. The *in vivo* sub-chronic phencyclidine (PCP) rat model of schizophrenia is well validated and induces robust deficits in cognition and short-term visual recognition memory, which can be measured using the Novel Object Recognition (NOR) behavioural task. Moreover, aerobic exercise therapy has been shown to increase hippocampal and plasma levels of brain-derived neurotrophic factor (BDNF), a protein that modulates synaptic change and long-term potentiation, thus providing a hypothesis for its therapeutic effects in schizophrenia[1,2].

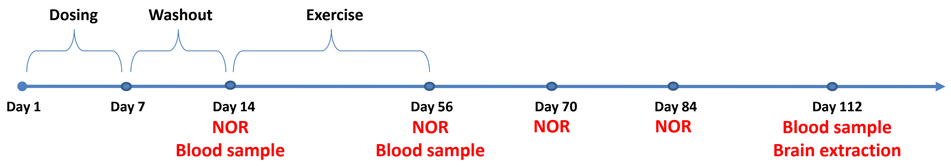
AIM: Our aim is to investigate the mechanisms of exercise-induced reversal of cognitive deficits in the scPCP model, with a focus on BDNF.

Methodology

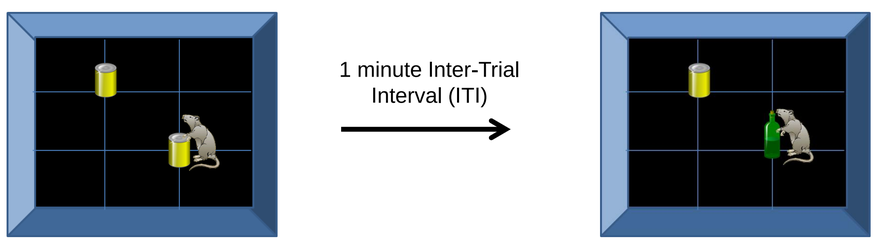


- Vehicle control (n=10)
- Vehicle exercise (n=10)
- PCP control (n=10)
- PCP exercise (n=10)

- 2mg/kg i.p. PCP or saline twice a day for 7 days
- 7 days washout period
- Exercise 1 hour/day, 5 days/week, for 6 weeks
- Locked wheels for control groups



Novel Object Recognition (NOR)



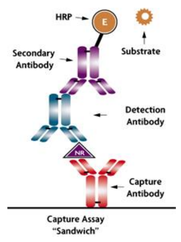
Blood Sampling

Blood sample → Centrifuge → Plasma extraction

- Lateral tail vein(s)
- EDTA-coated tubes
- 23G butterfly needles
- 10,000 RPM (10 minutes)
- Collected immediately following sampling
- Stored at -80°C

ELISA

- AVIVA Systems Biology (OKBB00128) BDNF ELISA kit



Specifications

Range	31.2 – 2,000 pg/mL
Sensitivity	< 2pg/mL
Specificity	Natural and recombinant rat BDNF
Cross-reactivity	No detectable cross-reactivity with relevant proteins

Results

Novel Object Recognition (NOR)

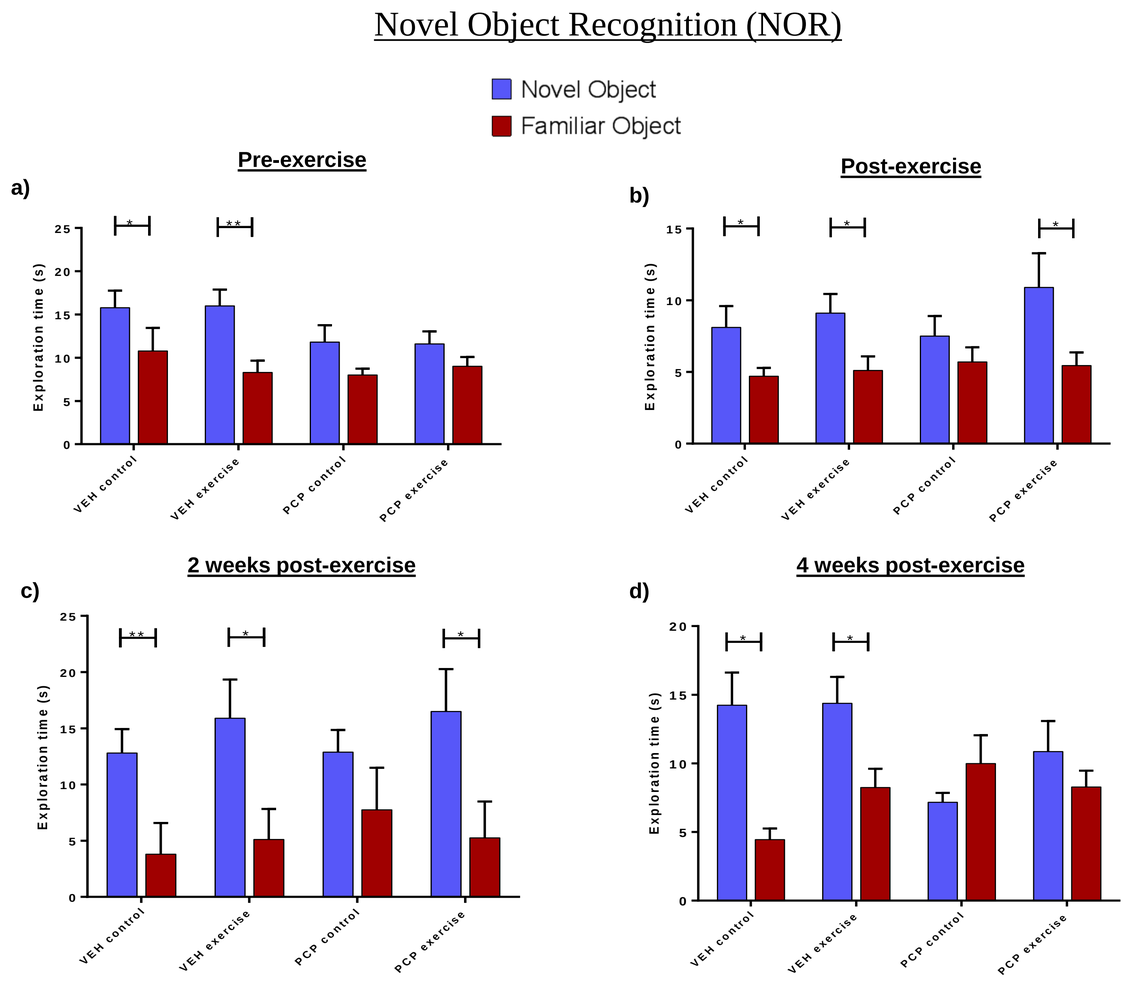


Figure 1 – All vehicle groups were able to discriminate between the novel and familiar objects across all time points (P<0.05). **a)** Pre-exercise NOR. An object recognition memory deficit is present in both PCP groups as they were not able to discriminate between the novel and familiar objects. **b)** Post-exercise NOR. While the PCP control group showed an object recognition memory deficit, the PCP exercise group was able to discriminate between the novel and familiar objects (P<0.05). **c)** 2 weeks post-exercise NOR. While the PCP control group showed an object recognition memory deficit, the PCP exercise group did not (P<0.05). **d)** 4 weeks post-exercise NOR. An object recognition memory deficit is present in both PCP groups. * P<0.05, ** P<0.01.

Plasma BDNF concentration (pg/mL)

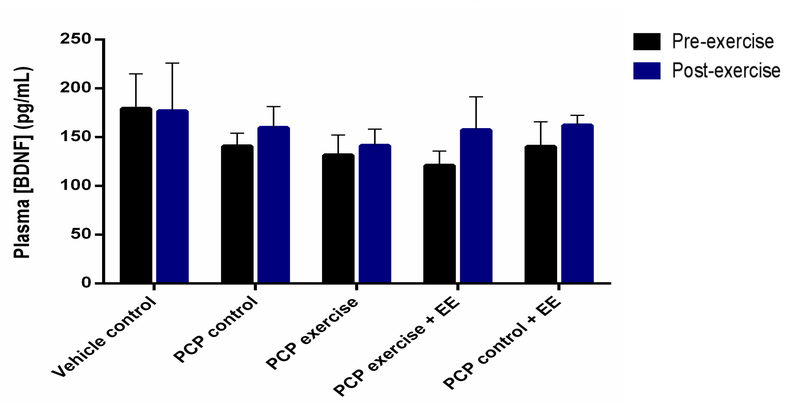


Figure 2 – Plasma BDNF concentration pre-exercise and after 6 weeks of exercise. Analysis of ELISA data showed no statistical differences in BDNF concentration pre-exercise and post-exercise, although average BDNF levels were elevated in intervention groups.

Exercise data

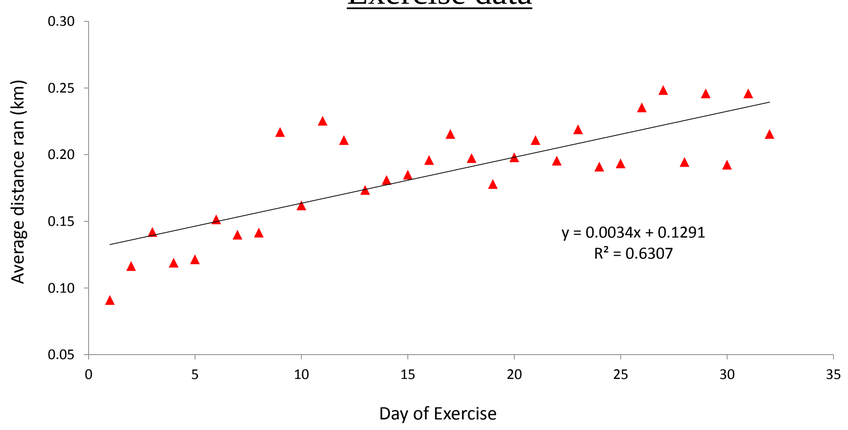


Figure 3 – Average distance ran by subjects throughout the course of 6 weeks of aerobic exercise. There is no statistical difference between the average distance ran by the vehicle and PCP groups.

Discussion

This work demonstrates that aerobic exercise reverses a robust cognitive deficit in a rat model for cognitive deficits of relevance to schizophrenia. The therapeutic effect of exercise was sustained 2 weeks post-exercise, but at 4 weeks post-exercise the cognitive deficit was present. Plasma analysis failed to show a significant post-exercise increase in BDNF levels, which may be a result of low sample sizes or poor quality plasma. Future work will involve the quantitative analysis of hippocampal, and pre-frontal cortex BDNF levels. Our work to evaluate potential mechanisms of the therapeutic effect of exercise through BDNF could inform future therapeutic strategies in patients.

References

1. Rasmussen, Peter, et al. "Evidence for a release of brain-derived neurotrophic factor from the brain during exercise." *Experimental physiology*94.10 (2009): 1062-1069.

2. Piepmeier, Aaron T., and Jennifer L. Etnier. "Brain-derived neurotrophic factor (BDNF) as a potential mechanism of the effects of acute exercise on cognitive performance." Journal of Sport and Health Science 4.1 (2015): 14-23.

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