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

Antonio J. Gonzalez, Lisa M. Heaney, Giovanni Podda, Joanna M. Oladipo, Ben Grayson, Michael K. Harte, Charles Large, Joanna C. Neill

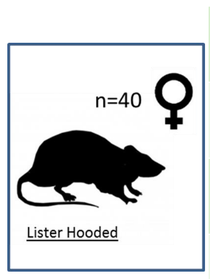
1) Division of Pharmacy & Optometry and School of Biology, Faculty of Biology, Medicine and Health, University of Manchester, Oxford road, Manchester, M13 9PT, UK
2) Autifony Therapeutics Ltd, Stevenage Bioscience Catalyst Incubator, Gunnels Wood Road, Stevenage, Herts.SG1 2FX, UK

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 on cognition in schizophrenia[1,2].

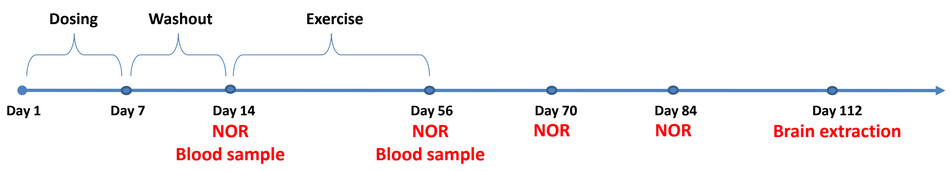
AIM: Our aim is to investigate the mechanisms of exercise-induced reversal of cognitive deficits in the scPCP model, with a focus on BDNF.

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



Phencyclidine model of cognition

PCP antagonism of GABAergic interneurons results in a loss of inhibitory input into glutamatergic pyramidal cells in the dorsolateral prefrontal cortex (DLPFC)

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Working memory is dependant on the sustained, controlled firing of glutamatergic pyramidal cells in the DLPFC

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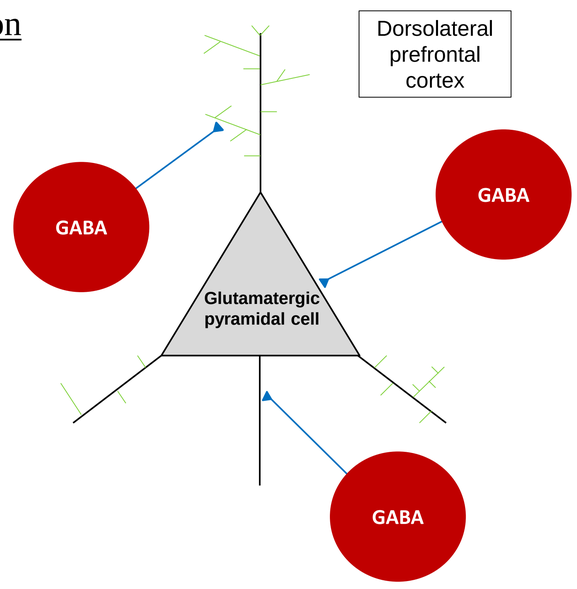
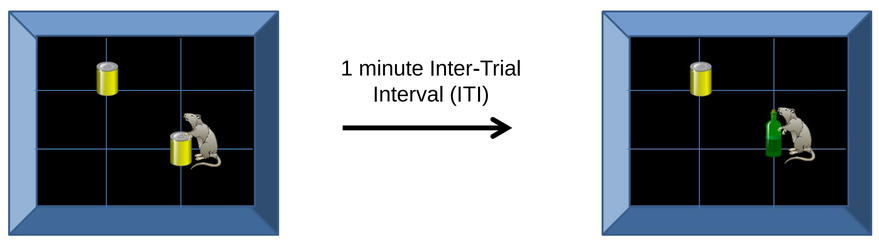
Dysregulated glutamatergic firing results in cognitive deficits



Novel Object Recognition (NOR)



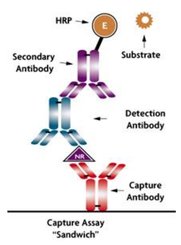
Blood Sampling

Blood sample → Centrifuge → Plasma extraction

- Sampled from lateral tail vein(s) with 23G needle
- Blood centrifuged at 10,000RPM for 10 minutes
- Plasma immediately collected and 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)

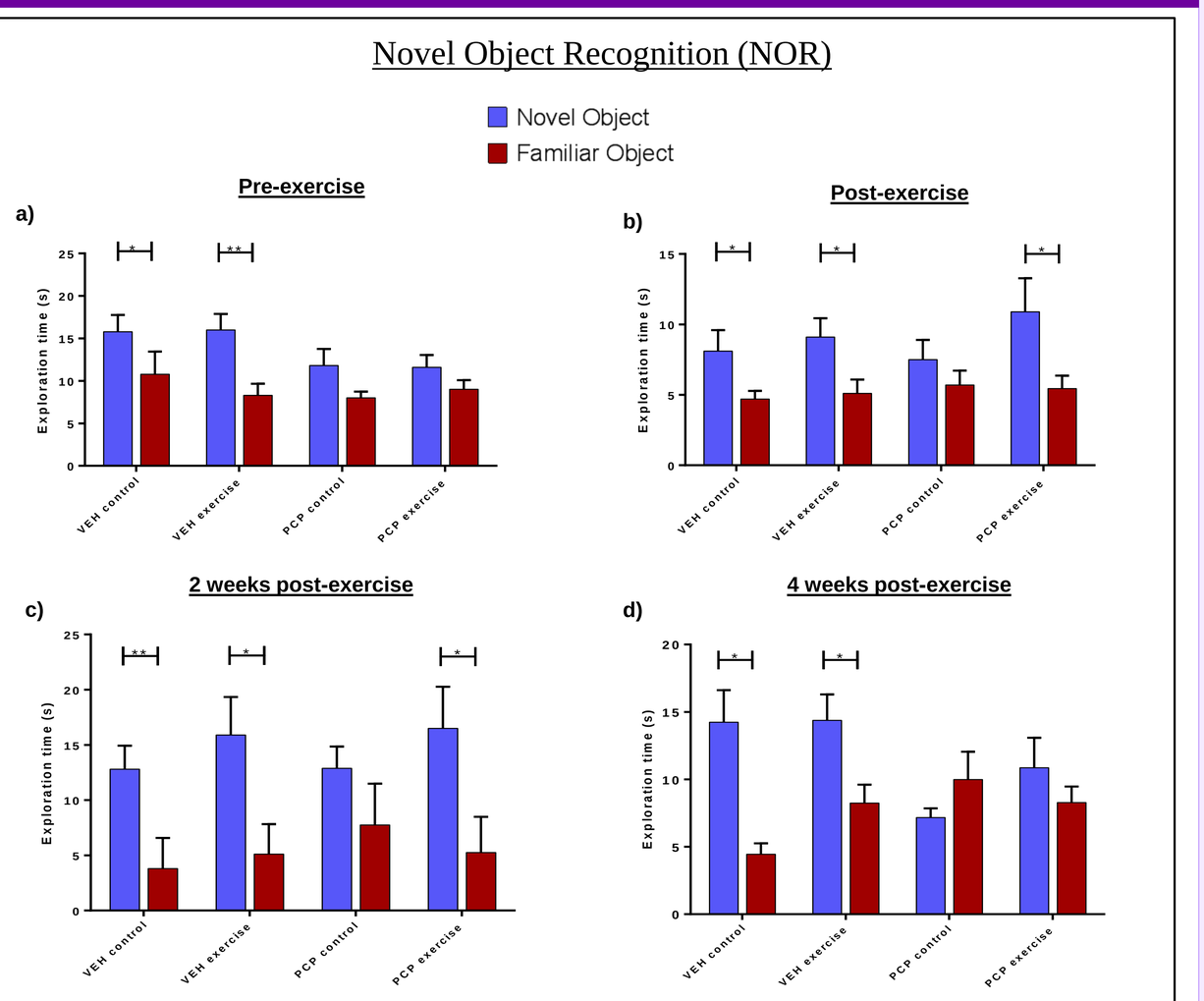


Figure 1 – All vehicle groups were able to discriminate between the novel and familiar objects across all time points (P<0.05). **a)** Pre-exercise NOR. An object recognition memory deficit is present in both PCP groups as they were not able to discriminate between the novel and familiar objects. **b)** 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)

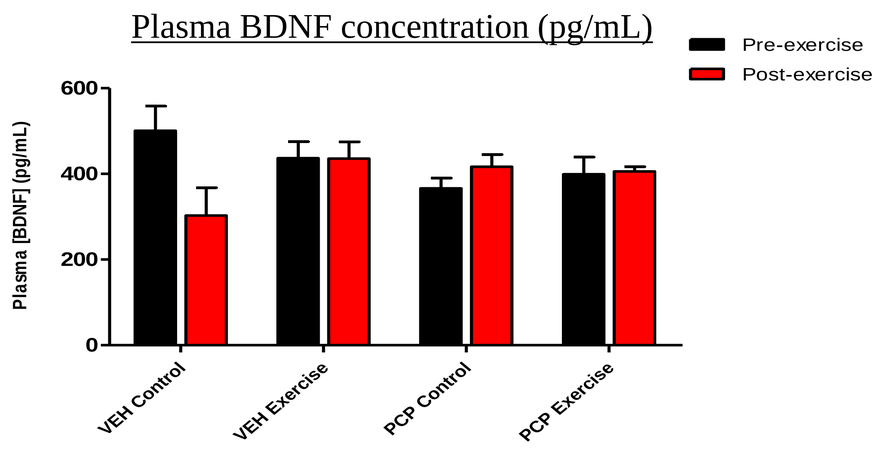


Figure 2 – Plasma BDNF concentration pre-exercise and after 6 weeks of exercise. Analysis of ELISA data showed no statistical differences in BDNF concentration pre-exercise and post-exercise.

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 again. 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 (protein and mRNA). Our work to evaluate potential mechanisms of the therapeutic effect of exercise through BDNF or other mediators 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.