Gym rats: exercise rescues the novel object recognition deficit in the sub-chronic PCP rat model for schizophrenia

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Background
Schizophrenia is a serious mental illness that affects around 1 in 100 people worldwide¹. Cognitive deficits are a core feature of the disease² and greatly reduce quality of life¹. There is currently no pharmacological treatment for cognitive deficits, making them an unmet clinical need. Exercise can alleviate cognitive deficits in people with schizophrenia³, but the mechanisms(s) by which it does are unclear.

The sub-chronic phencyclidine (PCP) rat model is a validated and widely-used tool in the study of schizophrenia⁴. The novel object recognition (NOR) task is used to assess cognition in rats. The PCP model can be used to investigate the possible pro-cognitive effects of exercise in schizophrenia.

Aims
The aim of this experiment was to investigate if voluntary wheel running can reverse the cognitive deficits observed in the NOR task in the sub-chronic PCP rat model of schizophrenia.

Methods and Materials

Sub-chronic phencyclidine (PCP) model

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<th>Twice daily PCP dose</th>
<th>Washout period</th>
<th>Behavioural Testing</th>
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<td>(2mg/kg) i.p. 09:00 and 16:30</td>
<td>40±10 s.c. saline 20x PCP</td>
<td>38±10 s.c. PCP 20x PCP</td>
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Deficits Observed

Veh or PCP Treatment | Washout Period | Cognitive Testing T1 | Wheel Running Intervention | Cognitive Testing T2 |
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<tr>
<td>Veh</td>
<td>0±10 s.c. placebo</td>
<td>0±10 s.c. PCP</td>
<td>Voluntary wheel running 1 day, 5 days rest, 2 days rest or control</td>
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</tr>
<tr>
<td>PCP</td>
<td>40±10 s.c. saline</td>
<td>0±10 s.c. PCP</td>
<td>Voluntary wheel running 1 day, 5 days rest, 2 days rest or control</td>
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Vehicle Control: Vehicle treatment + condition control (red plastic tunnel)

Vehicle Run: Vehicle treatment + voluntary wheel running

PCP Control: PCP treatment + condition control (red plastic tunnel)

PCP Run: PCP treatment + voluntary wheel running

Figure 1: NOR T1 A) In the acquisition phase, both groups spent an equal amount of time exploring the left and right objects. B) In the retention phase, Veh treated animals spent significantly more time exploring the novel object (n=20, p<0.05), an effect that was also present but significantly reduced (as measured by DI, see figure 2) in the PCP treated animals (n=20, p<0.05).

NOR T2 C) In the acquisition phase all groups spent an equal amount of time exploring the left and right objects. D) In the retention phase, both vehicle groups (Veh/Con; n=20, p<0.01) and Veh/Run (n=10, p<0.05) and the PCP/Run group (n=10, p<0.01) spent significantly more time exploring the novel over the familiar object. An effect that was not observed in the PCP/Con group.

Figure 2: NOR T1 E) Pre exercise/control the PCP group (n=20) and had a significantly lower DI than the vehicle group (n=20, p<0.01). NOR T2 F) Post exercise/control the PCP/Con group (n=10) had a significantly lower DI than the PCP/Run (n=10, p<0.01) and the Veh/Con groups (n=10, p<0.05). The was no difference in DI between the PCP/Con and Veh/Run groups.

Discussion and Future Work
We demonstrated that voluntary wheel running reversed the cognitive deficit, and restored the preference for a novel object, in the sub-chronic PCP rat model for schizophrenia. The brains of the animals will be analysed to investigate the potential mechanisms by which exercise ameliorates cognitive deficits in this model.

Cognitive deficits in schizophrenia remain a vital unmet clinical need. Understanding the pro-cognitive effects of exercise in the sub-chronic PCP rat model for schizophrenia may further our understanding of the effect of exercise in the clinic. Through this understanding, we may be able to identify novel pharmacological targets for treatment.

References
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⁶ Grayson, B. et al., NMDA antagonism attenuates a sub-chronic PCP-induced cognitive deficit in the novel object recognition task in the rat. Behavioural brain research, 2007; 184(1): p. 31-36

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