The sub-chronic phencyclidine (scPCP) model for schizophrenia induces deficits in non-spatial working memory, assessed by the Odour Span Task

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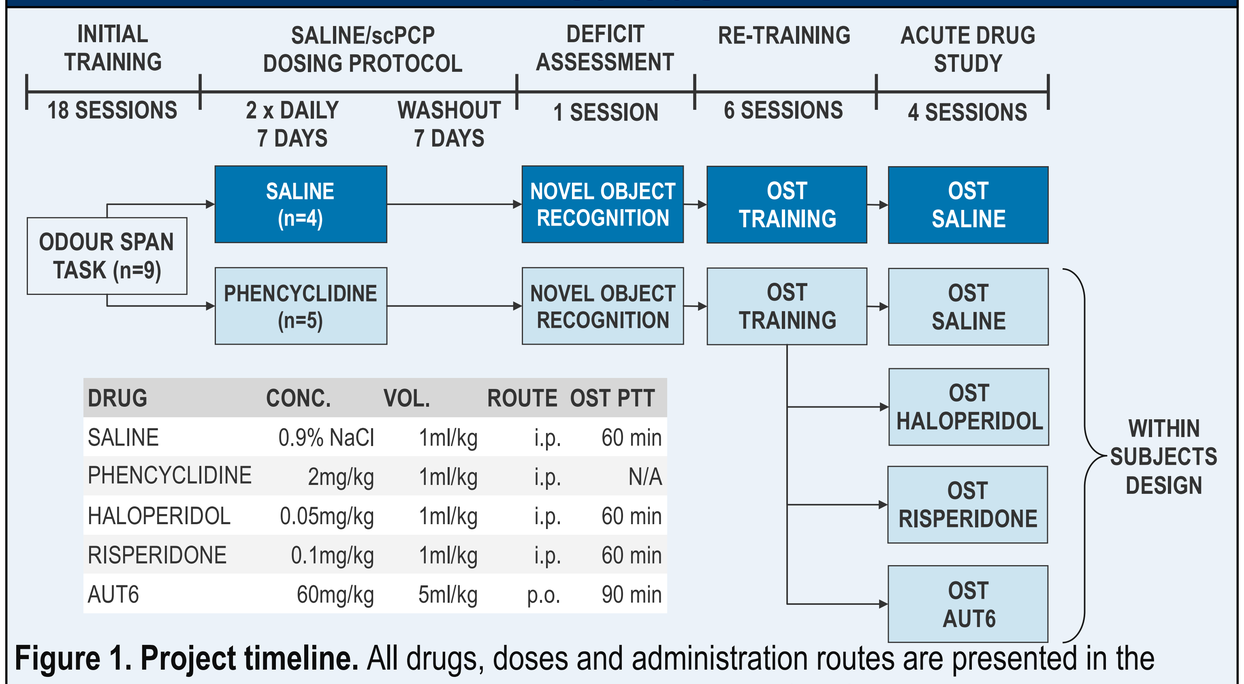
Introduction

- Schizophrenia patients often present with deficits in working memory, or "short term memory for an object, stimulus or location" (Dudchenko, 2004).
- The Odour Span Task was designed to assess non-spatial working memory capacity in rodents, localised to the prefrontal cortex (Dudchenko *et al*., 2000).
- Recent studies in the Neill laboratory show that sub-chronic phencyclidine (scPCP) administration results in robust deficits across multiple cognitive domains in female Lister Hooded rats. (Cadinu *et al.,* 2017)
- **The aim of this project was to validate the Odour Span Task as a method of assessing the non-spatial working memory capabilities of female Lister Hooded rats in the sub-chronic phencyclidine model for schizophrenia**
- **Typical (haloperidol), atypical (risperidone) and novel (AUT6) antipsychotics were administered in attempts to recover the scPCP induced deficits.**

Methods



DRUG	CONC.	VOL.	ROUTE	OST PTT
SALINE	0.9% NaCl	1ml/kg	i.p.	60 min
PHENCYCLIDINE	2mg/kg	1ml/kg	i.p.	N/A
HALOPERIDOL	0.05mg/kg	1ml/kg	i.p.	60 min
RISPERIDONE	0.1mg/kg	1ml/kg	i.p.	60 min
AUT6	60mg/kg	5ml/kg	p.o.	90 min

Figure 1. Project timeline. All drugs, doses and administration routes are presented in the above table. For the acute drug study, the pre-treatment time (PTT) is also presented.

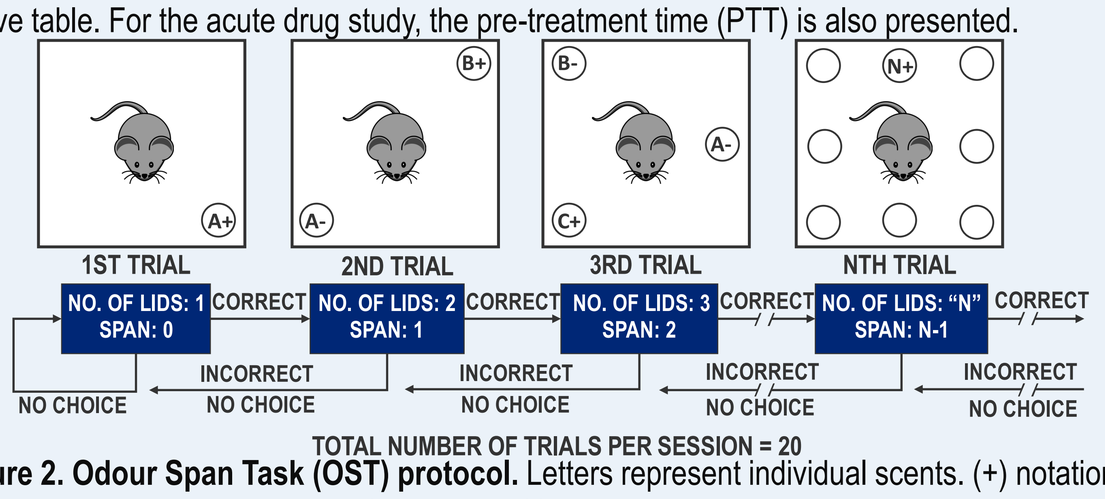


Figure 2. Odour Span Task (OST) protocol. Letters represent individual scents. (+) notation represent the novel, baited scent for this trial. (-) notation represents a previously used, non-baited scent. Correct identification of the novel scent advances trials, increasing the number of odours present with each consecutive correct choice. Incorrect choices, or absence of choices within 2 minutes, resets the trials back to the 1st trial. **Span = the number of correctly identified scents in a row – 1.**

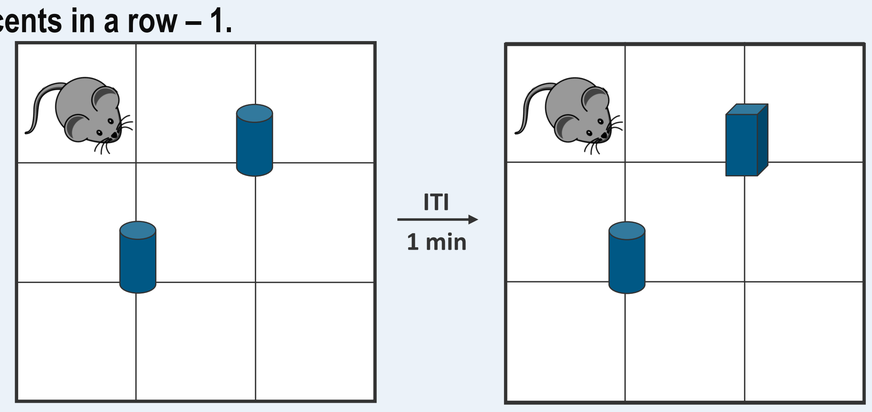


Figure 3. Novel Object Recognition (NOR) task protocol. Rats were placed in an arena containing two identical objects, and were allowed to explore. Rats were then removed for a 1 minute inter trial interval. Rats were placed back into the arena containing a triplicate of the first objects, and a novel object, and were allowed to explore. Object exploration time was recorded. **Discrimination Index = (novel -familiar exploration (s))/(novel + familiar exploration (s)).**

Results

Data are presented as mean ± SEM. For OST results, both the first span achieved per session and the highest span achieved per session are presented. Sessions were completed once per day (Monday to Friday).

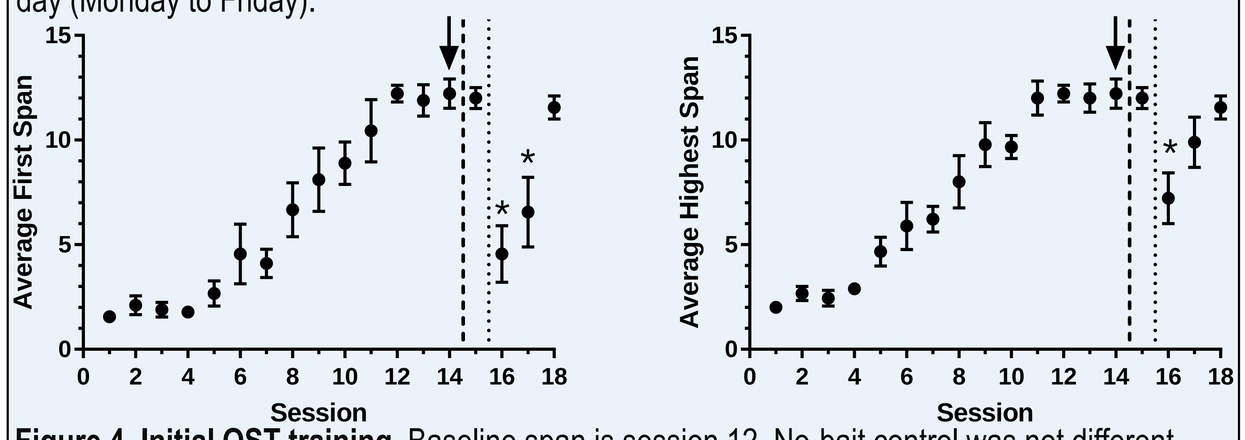


Figure 4. Initial OST training. Baseline span is session 12. No-bait control was not different from baseline. Span after a 7-day gap in training (session 15) was not different from baseline. Span after a 14-day gap in training (session 16) was significantly lower than baseline (*p<0.05) requiring two additional sessions to return to baseline. Friedman test with Dunn's multiple comparisons tests.

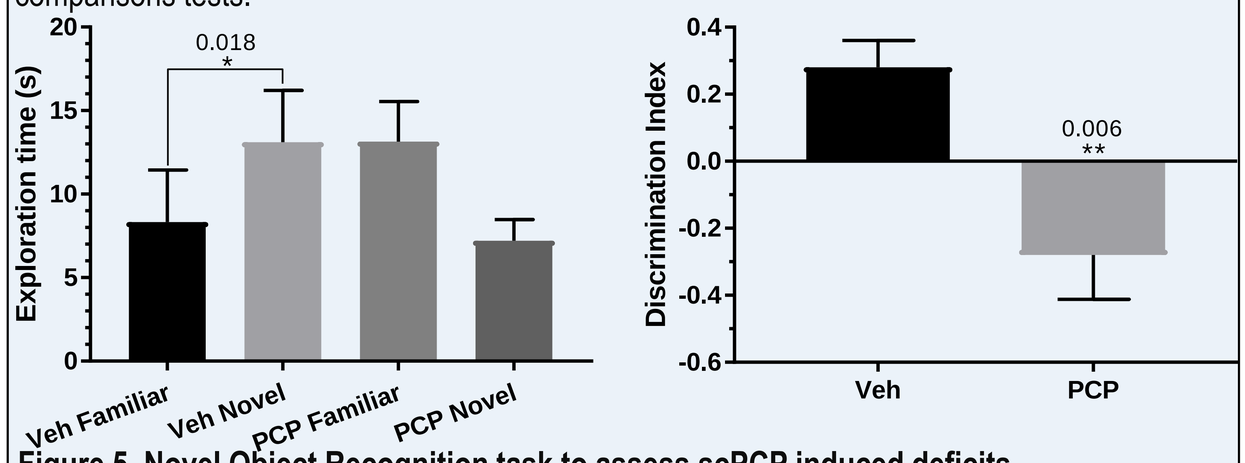


Figure 5. Novel Object Recognition task to assess scPCP induced deficits. Vehicle (saline) treated rats explored the novel object significantly more than the familiar. scPCP rats showed equal exploration of novel and familiar objects. DI shows scPCP rats preferentially explored the familiar object, whereas vehicle-treated rats the novel object.

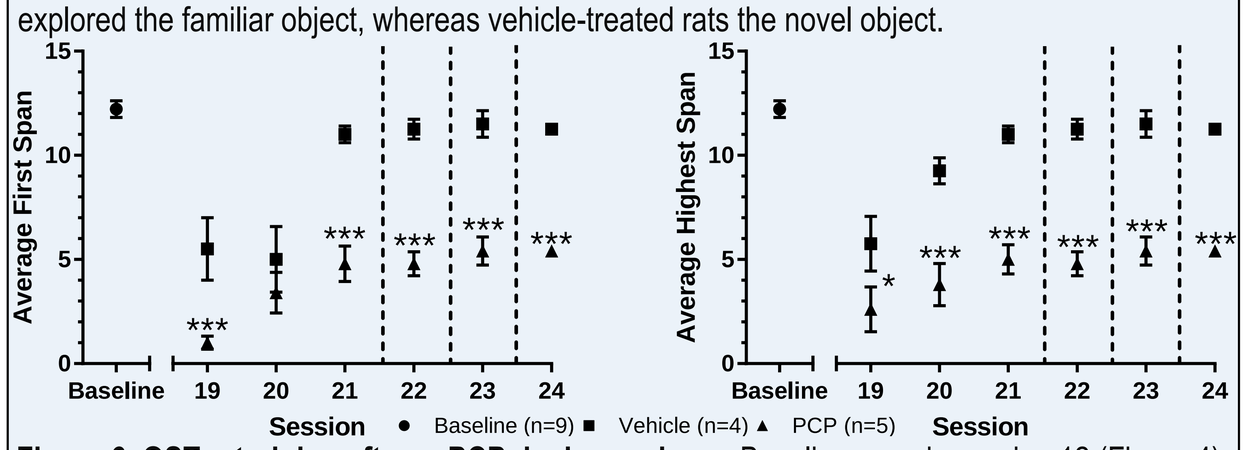


Figure 6. OST retraining after scPCP dosing regimen. Baseline span is session 12 (Figure 4). Session 22, 23 and 24 each took place after a 7 day break in training (dashed line) testing span stability. Vehicle-treated rats returned to baseline after 3 training sessions (session 21). PCP-treated rats spans were significantly lower than vehicle spans for each training session (*p<0.05; ** p<0.01; *** p<0.001). 2-way ANOVA with Sidak's multiple comparisons test.

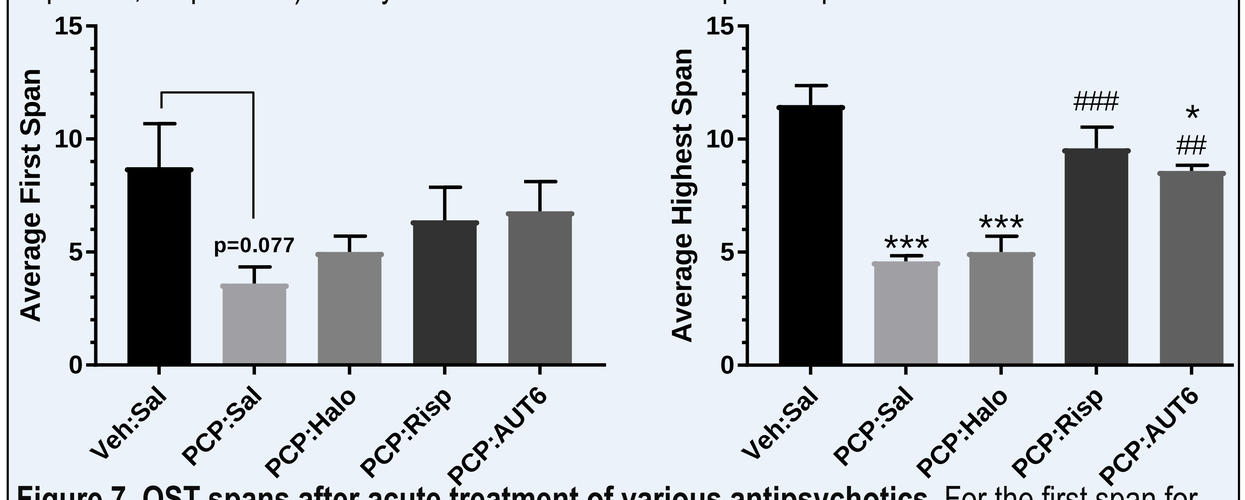


Figure 7. OST spans after acute treatment of various antipsychotics. For the first span for each session, no significance was seen between treatment groups. When analysing the highest span for each sessions, scPCP-treated rats dosed with saline, haloperidol, or AUT6 showed significantly lower spans when compared to the vehicle:saline control. (* p<0.05; *** p<0.001). scPCP-treated rats dosed with risperidone or AUT6 scored significantly higher spans than scPCP saline controls (## p<0.01; ### p<0.001). 1-way ANOVA with Tukey test.

Conclusion

- The OST appears to show a potential maximal working memory capacity after 12 training sessions that remains stable after a 7-day gap in training
- Sub-chronic administration of sub-chronic phencyclidine induced robust cognitive deficits, assessed by the NOR task.
- First span and highest span per session report different results
- scPCP-treated rats exhibit significantly lower working memory capacity
- Haloperidol did not alter the scPCP rats working memory capacity
- Risperidone significantly increases scPCP rats working memory capacity
- AUT6 significantly increases scPCP rats working memory capacity
- The OST appears to be a valid method for assessing working memory capacity

References: Cadinu, D., Grayson, B., Podda, G., Harte, M.K., Doostdar, N. and Neill, J.C. 2018. NMDA receptor antagonist rodent models for cognition in schizophrenia and identification of novel drug treatments, an update. *Neuropharmacology*. **128**(3),pp.419–432. **Dudchenko, P.A**. 2004. An overview of the tasks used to test working memory in rodents. *Neuroscience and Biobehavioral Reviews*. **28**(7),pp.699–709. **Dudchenko, P.A.,** Wood, E.R. and Eichenbaum, H. 2000. Neurotoxic hippocampal lesions have no effect on odor span and little effect on odor recognition memory but produce significant impairments on spatial span, recognition, and alternation. *Journal of Neuroscience*. **20**(8),pp.2964–2977.