

Investigation into spatial working memory deficits in the sub-chronic phencyclidine (scPCP) rat model for schizophrenia

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1. Introduction

- The scPCP model for schizophrenia in rats has been shown to mimic the negative symptoms, cognitive deficits and pathological changes seen in the prefrontal cortex and hippocampus of schizophrenia patients.¹
- These include attention, executive function, visual recognition memory, and problem solving have been shown.¹
- It is not yet known whether scPCP treatment causes a spatial working memory deficit in rats.

The aim of this study was to demonstrate whether spatial working memory is impaired in the scPCP model for schizophrenia in rats using the radial arm maze.

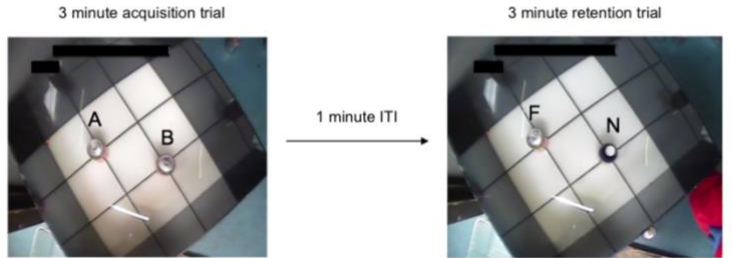
2. Methods

Dosing: Following RAM training: rats were given either scPCP (2 mg/kg, i.p.) or vehicle (0.9% saline) twice daily for seven days, followed by at least a 7-day washout period (n=10 per group).

8-Arm Radial Maze (RAM): 10 training sessions and 3 experimental sessions. All arms baited, trials last until all arms visited or a maximum of 8 minutes. The number of arm re-entries, time taken for all 8 arms to be entered, the total number of arms entered, and which arms were entered in 8 minutes were recorded.



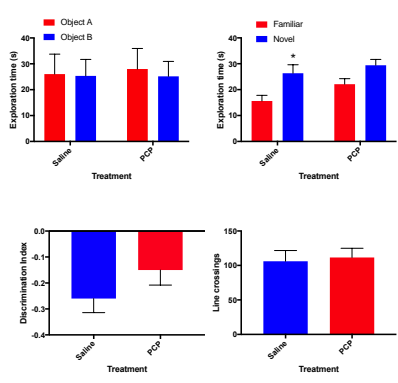
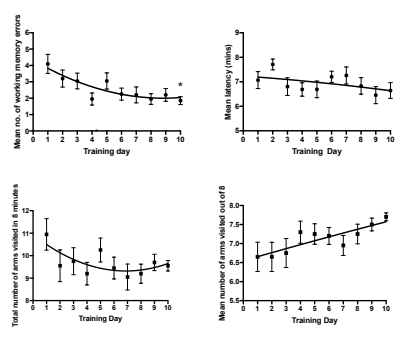
Novel Object Recognition (NOR): Acquisition trial contains object A and B. Retention trial contains the familiar (F) and novel (N) object. Exploration time of each object and the number of line crossings was measured.



3a. Results: Training and NOR

10 days of training causes rats to make less WM errors in the RAM.

- Training in the RAM reduces the number of working memory errors made.
- No effect on time taken to visit all 8 arms, the total number of arms visited nor the number of the 8 arms visited.



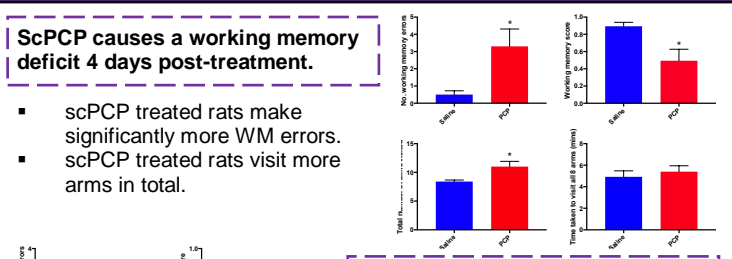
scPCP treatment causes a reference memory deficit.

- No difference between exploration time of object A or B for vehicle or scPCP treated rats.
- No difference between exploration time of familiar and novel object in scPCP treated rats.
- No effect on activity.

3b. Results: RAM

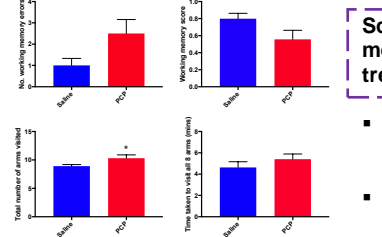
scPCP causes a working memory deficit 4 days post-treatment.

- scPCP treated rats make significantly more WM errors.
- scPCP treated rats visit more arms in total.



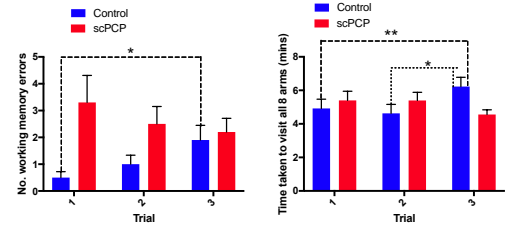
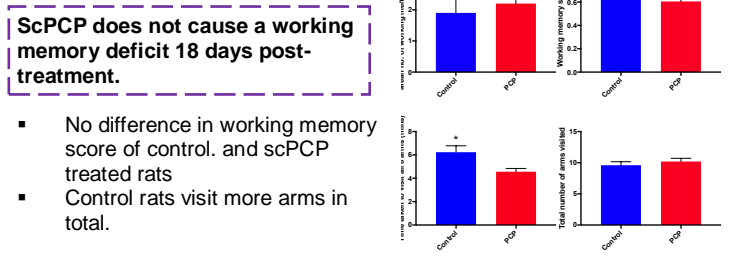
scPCP does not cause a working memory deficit 8 days post-treatment.

- scPCP treated rats perform better than 1st trial, control rats perform worse.
- scPCP treated rats visit more arms in total.



scPCP does not cause a working memory deficit 18 days post-treatment.

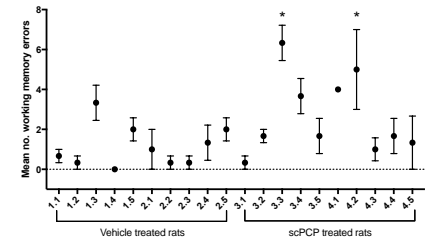
- No difference in working memory score of control and scPCP treated rats.
- Control rats visit more arms in total.



Control rats performed worse over time and scPCP treated rats improved over time.

Two scPCP treated rats showed significant working memory deficits over the 3 trials.

- Large variability between individual rats in both control and scPCP rats.



4. Conclusion

- A robust spatial working memory deficit was not observed in our animal model in the RAM.
- Confirmation of a WM deficit will support the use of this model to identify novel treatments to restore WM deficits in schizophrenia and other disorders with cortical and hippocampal dysfunction.
- Evidence that the 8-arm RAM is not suitable due to large variability between individuals and only minor improvements on WM after training.

Revision of the RAM protocol may provide more robust evidence of a spatial working memory deficit in the scPCP animal model for schizophrenia.

5. References

¹ Cadinu, D., Grayson, B., Podda, G., Harte, M. K., Doostdar, N., Neill, J. C. (2017). NMDA receptor antagonist rodent models for cognition in schizophrenia and identification of novel drug treatments, an update. *Neuropharmacology*, <https://doi.org/10.1016/j.neuropharm.2017.11.045>.