# THE GPR52 AGONIST HTL0041178 ATTENUATES REVERSAL LEARNING DEFICITS IN THE SUB-CHRONIC PHENCYCLIDINE RAT

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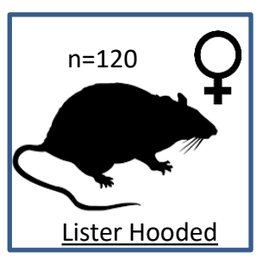
## Introduction

- 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 sub-chronic phencyclidine (scPCP) rat model for schizophrenia is well validated and induces robust deficits in several domains of cognition including prefrontal executive function, which can be measured using the operant Reversal Learning (RL) task (see review by Cadinu et al, 2018).
- GPR52 is a Gαs coupled orphan G-protein coupled receptor (GPCR), highly expressed on both dopamine D1 cortical pyramidal neurons and D2 striatal medium spiny neurons (Sawzdargo et al., 1999). Altered frontocortical D1 receptor availability has been suggested to contribute to cognitive impairments associated with schizophrenia (CIAS; Abi-Dargham, 2003). Recent findings revealed that depending on receptor localisation, a GPR52 agonist can act like a dopamine D1 receptor activator or inhibitor of dopamine D2 receptor function (Komatsu et al, 2014), and may therefore improve both the cognitive and positive symptoms of schizophrenia (Nishiyama et al, 2017).
- Here we investigate the effect of a novel selective GPR52 receptor agonist, HTL0041178 (Watson, 2021), and compared its effects to the D1 receptor agonist, SKF-38393, and the D2 receptor antagonist, fluphenazine, in our scPCP model for CIAS.

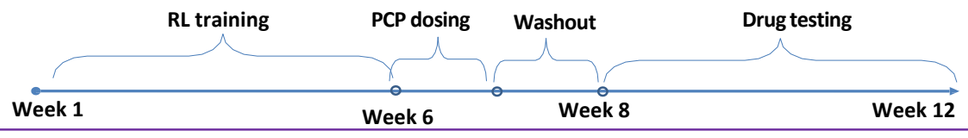
## Methods




**scVeh (n=20)**

**scPCP (n=100)**

- **RL training (8 weeks)**
- **2mg/kg i.p. PCP or saline twice a day for 7 days**
- **7 days washout period**
- **Drug testing (HTL0041178, SKF-38393 & fluphenazine)**




• Two cohorts (C1 & C2) each consisting of 60 adult female Lister-hooded rats maintained at 90% free-feeding weight were trained to perform an operant RL task to 90% criterion by a method previously described in detail (Idris et al. 2010).

• After training both cohorts, rats were treated with PCP (n=50) at 2 mg/kg (i.p.) or vehicle (saline; n=10) twice daily for 7-days, followed by 7-days washout.

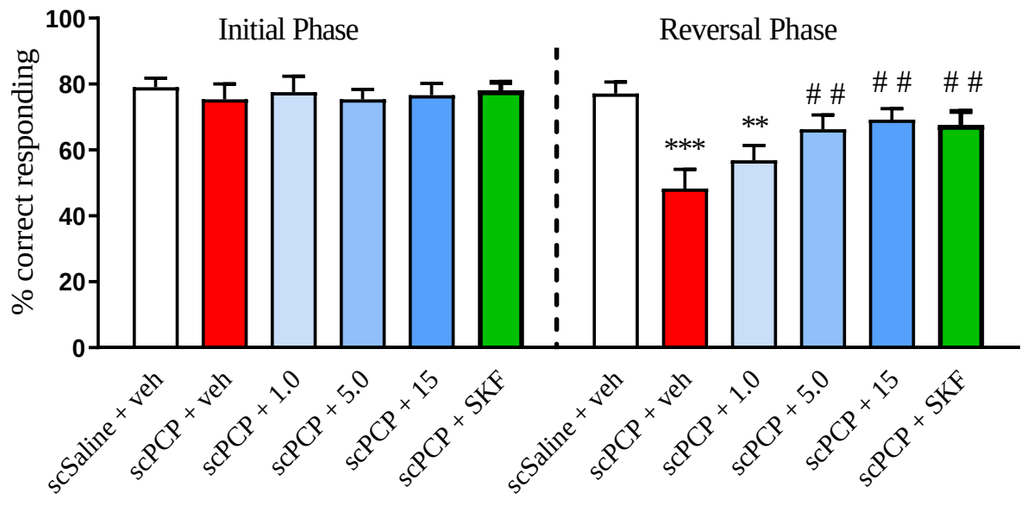
• Rats were then treated acutely with HTL0041178 (C1, experiments 1a: 1, 5 & 15 mg/kg and 1b: 3, 10 & 30 mg/kg, p.o. 2h prior to testing), fluphenazine (C2, experiment 2a: 0.1, 0.2 & 0.4 mg/kg, i.p. 1h prior to testing), SKF-38393 (cohort 2, experiment 2b: 0.75, 1.5, 3 & 6 mg/kg, i.p. 1h prior to testing), or vehicle and were tested in the RL task.

• The RL data was Arc-Sin transformed and expressed as mean ± SEM and analysed by ANOVA followed by post-hoc LSD t-test.

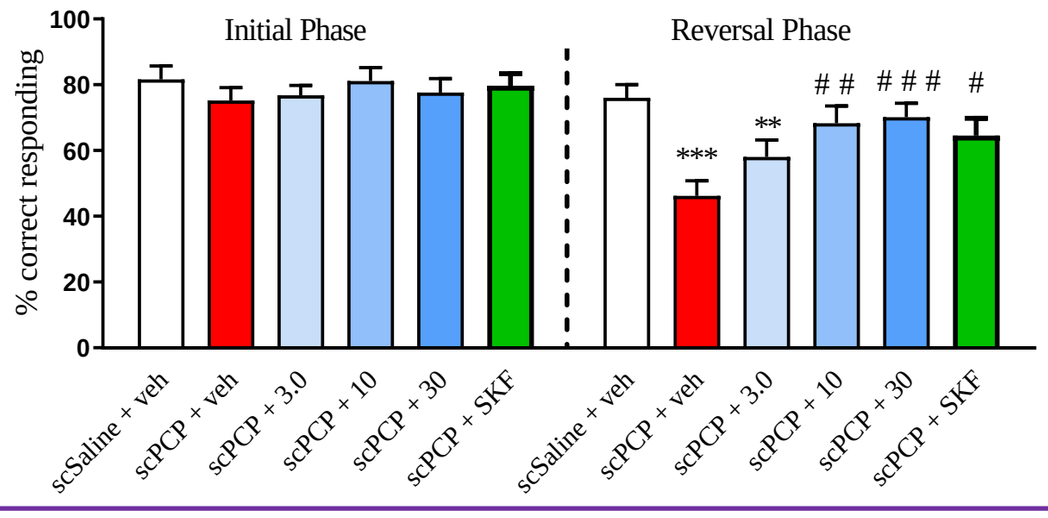
## Results

### The GPR52 agonist, HTL0041178, reversed the scPCP-induced deficit across a wide dose range.

**1a:**



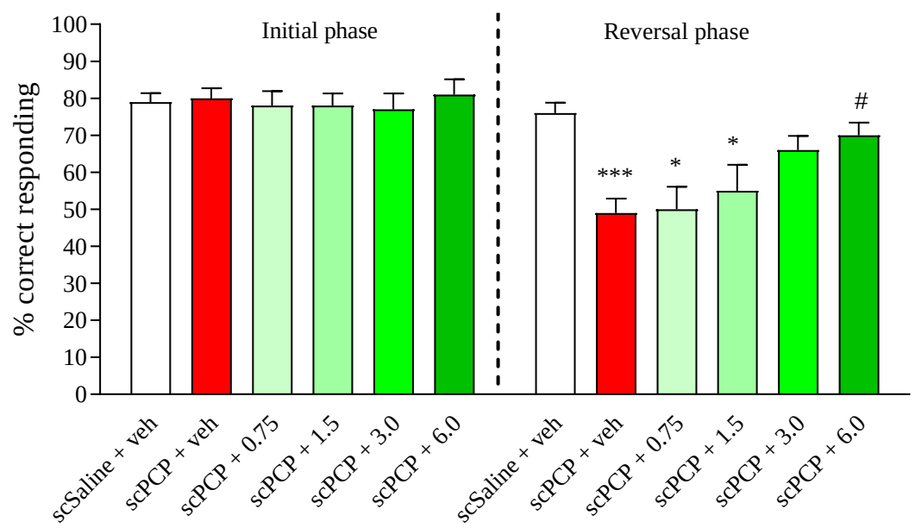

**1b:**




## Results

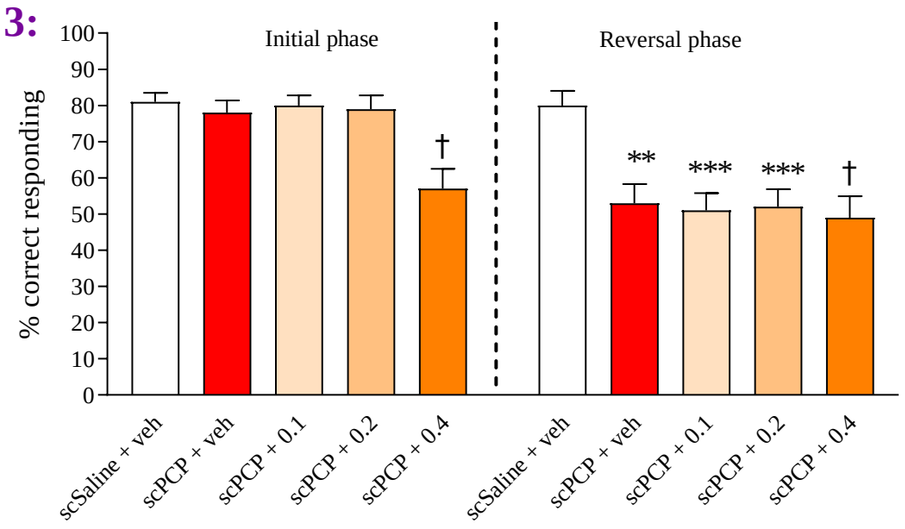
### The D1 receptor agonist, SKF-38393, reversed the scPCP-induced deficit.

**2:**




### The D2 receptor antagonist, fluphenazine, was ineffective against the scPCP-induced deficit.

**3:**




**Figures 1-2:**. Significant reduction in correct responding of drug treatment groups compared with vehicle group in the reversal phases; **P<0.01, ***P<0.001. Significant improvement in responding compared to scPCP in the reversal phases; #P<0.05, ##P<0.01, ###P<0.001 Significant reduction in performance of the initial and reversal phase compared with the respective vehicle group; †P<0.01. ANOVA followed by LSD t- test.

## Conclusions

• **scPCP** significantly (P<0.01-P<0.001) reduced percent correct responding compared to vehicle (Fig 1-2).

• **HTL0041178** (5-30 mg/kg) significantly (P<0.01-P<0.001) and dose dependently reversed the deficit induced by scPCP compared to vehicle (Fig 1a and 1b).

• **SKF-38393** (6 mg/kg) significantly (P<0.05) and dose dependently reversed the deficit induced by scPCP compared to vehicle (Fig 2a).

• **Fluphenazine** was unable to reverse the scPCP-induced deficit (Fig 2b).

These findings show that the D2 receptor antagonist, fluphenazine failed to reverse the scPCP induced deficit. However, the GPR52 agonist, HTL0041178 reversed the scPCP-induced RL deficit in a manner comparable to the D1 receptor agonist, SKF-38393 and support the progression of HTL0041178 as a potential effective treatment for CIAS.

## References

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