P.3.a.012: The GlyT1 inhibitor RO4993850 alters social behaviour and ultrasonic vocalisation calls in a neonatal-PCP isolation-reared rat model for schizophrenia

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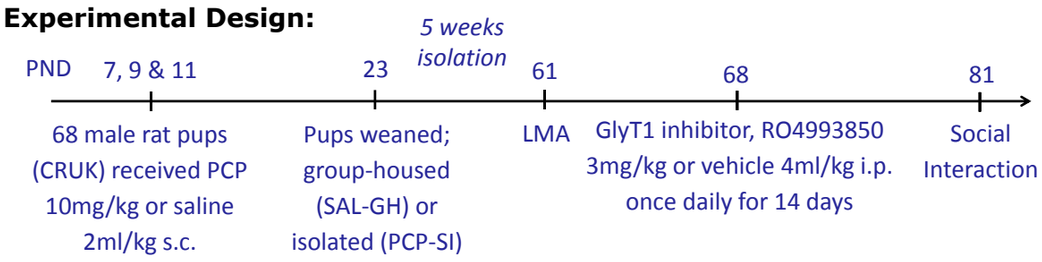
Introduction

- Neonatal PCP followed by social isolation rearing from weaning (a two-hit neurodevelopmental putative model for schizophrenia) produces behavioural, functional and neurochemical changes, which are akin to several core changes seen in schizophrenia.
- Glycine Transporter (GlyT1) inhibitors regulate synaptic levels of the NMDA receptor co-agonist glycine and therefore represent a potential treatment approach for disorders involving NMDA receptor hypofunction, such as schizophrenia, by indirectly enhancing NMDA receptor activity.
- The GlyT1 inhibitor bitopertin has been shown to improve negative symptom scores in patients with schizophrenia [1] and acute injection of RO4993850, an analogue of GlyT1 inhibitor bitopertin, improved social deficits in the current neurodevelopmental rat model [2]
- **This study determined if chronic administration of GlyT1-inhibitor RO4993850, could attenuate deficits in social behaviour and ultrasonic vocalisations (USVs) during social interaction in this rat neurodevelopmental model for schizophrenia.**

Methods

Experimental Design:



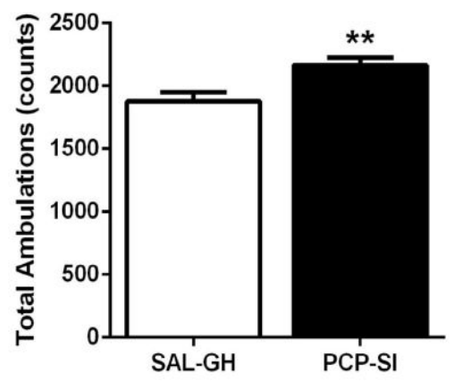
Locomotor Activity (LMA): Rats placed into a novel-arena for 60min

Social Interaction: Rats paired by weight (<30g), litter and treatment and placed into an open field arena for 10min

- **Social Behaviour:** scored post-trial using Ethovision (Noldus) video-tracking software
- **Ultrasonic Vocalisations (USVs):** Recorded during social interaction and call characteristics determined with Avisoft analysis software (SAS-Lab Pro, v 4.38, Avisoft Bioacoustic, Berlin)

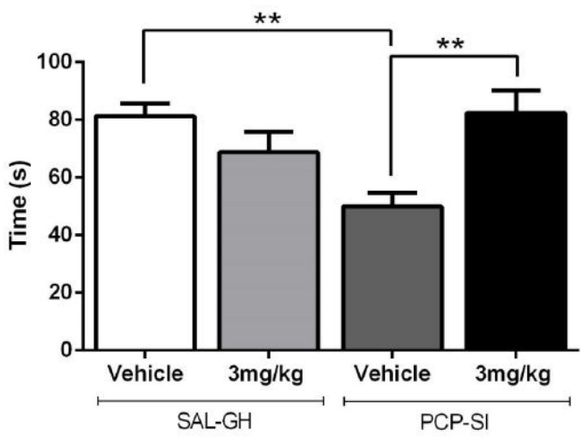
Results

LMA: PCP-SI were significantly hyperactive compared to SAL-GH



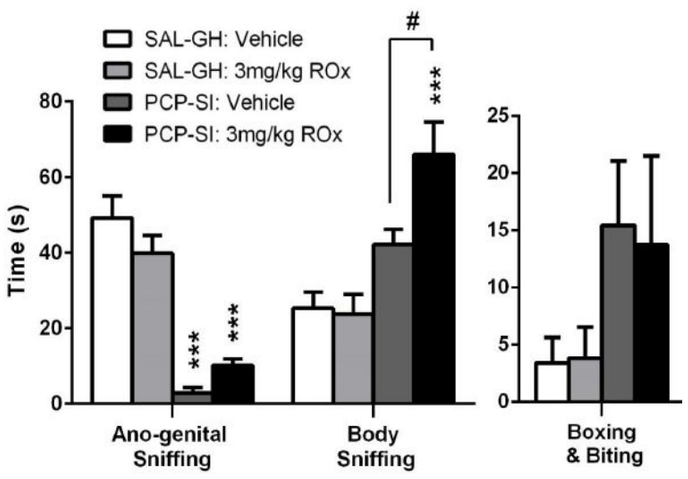
**p<0.01 compared to SAL-GH; *Sidak* post-hoc.

Social Interaction: Total Time Interacting



**p<0.01 PCP-SI Vehicle compared to SAL-GH Vehicle, or PCP-SI 3mg/kg compared to PCP-SI Vehicle; *Tukey* post-hoc

Social Interaction: Individual Component Behaviours

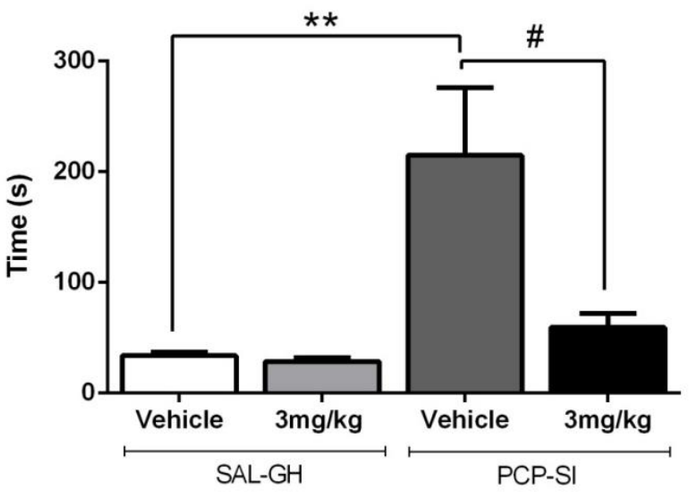


***p<0.001 compared to SAL-GH Vehicle, #p<0.05 compared to PCP-SI Vehicle; *Tukey* post-hoc

- PCP-SI displayed reduced overall pro-social interaction (all behaviours except boxing/biting) compared to SAL-GH rats.
- PCP-SI deficit was attenuated by RO4993850 such that there was a significant PCP/housing x treatment interaction ($F(1,29)=13.46$, $p=0.001$; two-way ANOVA) but no main effect of either alone.
- PCP-SI displayed significantly less ano-genital but more body sniffing and boxing/biting than SAL-GH controls; two-way ANOVA.
- RO4993850 significantly increased body sniffing in PCP-SI rats.

Results

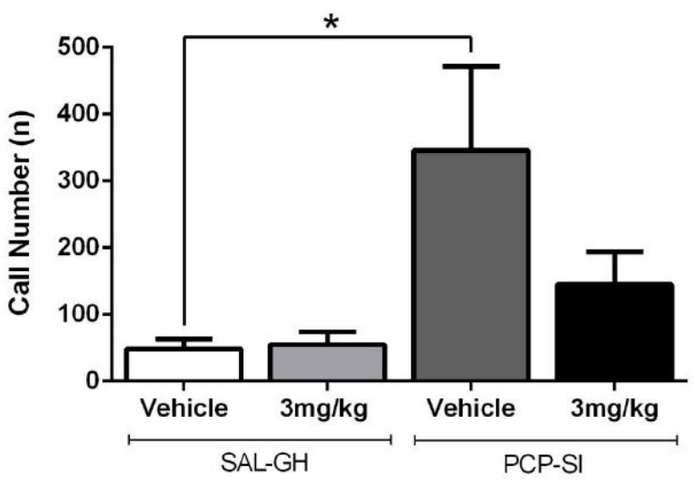
Social Interaction: Latency to first ano-genital sniffing interaction



**p<0.01 compared to SAL-GH Vehicle, #p<0.05 compared to PCP-SI Vehicle; Tukey post-hoc

PCP-SI took longer to engage in ano-genital sniffing than SAL-GH rats ($p=0.0043$), which was reduced by RO4993850 ($p=0.0257$; two-way ANOVA).

USVs: PCP-SI emitted significantly more 50kHz calls than SAL-GH

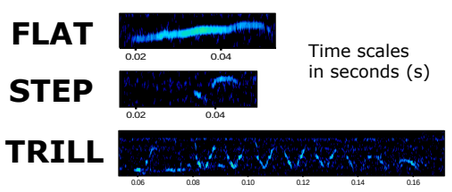


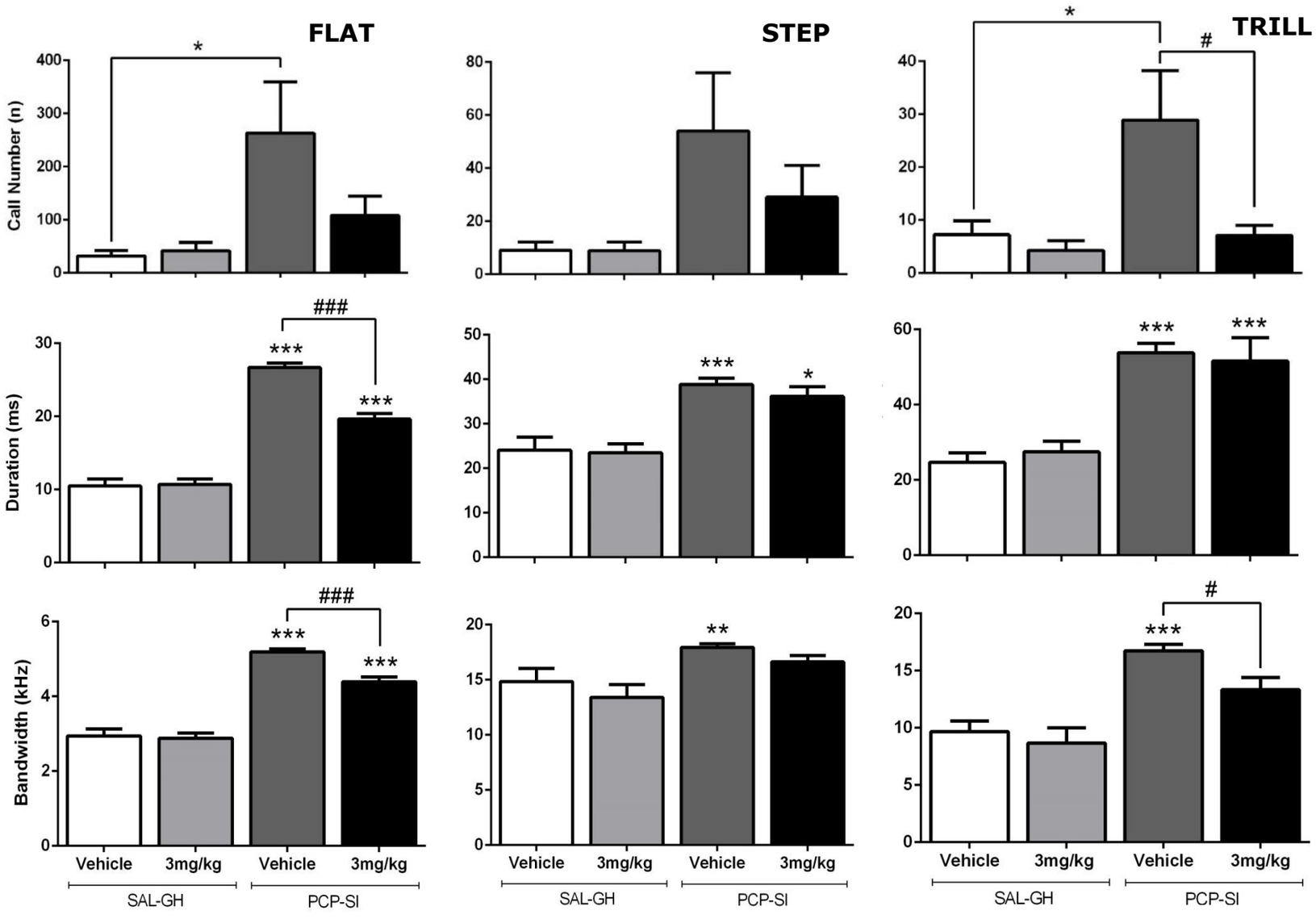
*p<0.05, compared to SAL-GH Vehicle; *Tukey* post-hoc.

USVs: Pattern Analysis

- PCP-SI rats emitted significantly more USVs in each call subtype; flat, step and trill, which were also longer in duration ($p<0.0001$; two-way ANOVA) than those emitted by SAL-GH controls.
- RO4993850 significantly reduced the number of trill calls in PCP-SI rats ($p<0.05$) and the mean duration of flat calls ($p<0.001$, Tukey post-hoc).

Call Subtypes:





*p<0.05, **p<0.01, ***p<0.001 compared to SAL-GH Vehicle, #p<0.05, ###p<0.001 compared to PCP-SI Vehicle; Sidak post-hoc.

Conclusions

- Neonatal-PCP isolation-rearing (PCP-SI) induces social impairments and alters social communication.
- Chronic treatment with RO4993850 attenuated some of these social deficits and altered USVs in PCP-SI rats without altering these effects in SAL-GH controls, suggesting that GlyT1 inhibitors are potential therapeutics for social deficits seen in psychiatric disorders such as schizophrenia and Autism Spectrum Disorders.

References

[1] Umbricht et al. (2014) Effect of bitopertin, a glycine reuptake inhibitor, on negative symptoms of schizophrenia: a randomized, double-blind, proof-of-concept study. JAMA Psychiatry, 71: 637-46

[2] McIntosh (2014) Modelling the negative symptoms of schizophrenia in the rat (doctoral thesis, University of Nottingham.

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