Differential effects of two mGlu5 positive allosteric modulators on cognition and prefrontal cortex signalling in the sub-chronic PCP animal model for schizophrenia.

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Introduction

- Disruption of glutamatergic signalling linked to NMDAR hypofunction has been associated with the core symptoms of schizophrenia. Endogenous glutamate activates mGlu5 receptors (mGluR5) expressed within key circuits in several brain regions.
- Our overall aim is to identify cell specific mGlu5-signalling pathways (figure 1) in brain regions (prefrontal cortex-PFC and hippocampus) involved in mediation of negative and cognitive symptoms in schizophrenia. The hypothesis is that mGlu5 receptor signalling is cell specific and distinctly coupled to various G-proteins in brain regions mediating these symptoms.
- Here we assess efficacy of two mGlu5 positive allosteric modulators (PAMs), VU0409551 and VU0360172 that exhibit *in vivo* efficacy in animal tests of antipsychotic activity (Sengmany *et al.*, 2017, PMID: 27392634) in our validated animal model for cognitive deficits and negative symptoms in schizophrenia (Cadinu et al. 2017, PMID: 29196183).

Our long-term aim is construction of a chemical library of compounds with brain area/ cell specific mGlu5 signalling profiles and consequently identification of therapeutic compounds with reduced adverse effects.

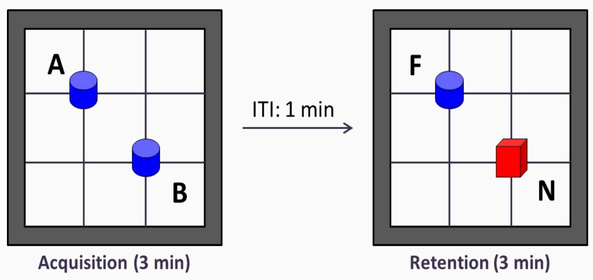
Methods

Female Lister Hooded rats received sub-chronic phencyclidine (scPCP; 2 mg/kg) or vehicle i.p. twice daily for 7 days, followed by at least 7 days washout.

Rats received VU0409551 or VU0360172, Tocris, UK (NOR: 1 & 10 mg/kg, i.p., SI: 10 mg/kg, i.p.) and were tested in novel object recognition (NOR) and social interaction (SI) tests.

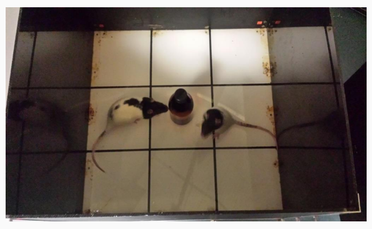
PFC and hippocampus were homogenised in Triton X-lysis buffer (Menna et al, 2018, PMID: 29079293), sonicated in ice and centrifuged. Protein cell lysates were separated by SDS-PAGE electrophoresis, blotted onto nitrocellulose followed by a Western blot analysis of p-AKT and p-ERK1/2.

Novel object recognition
Cohort 1



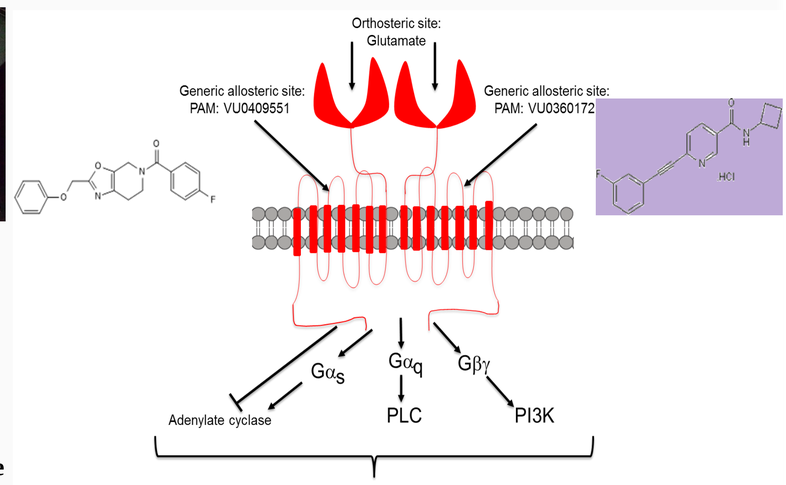
Cognition

Social interaction
Cohort 2



Negative symptoms

mGlu5 signalling
Cohort 1

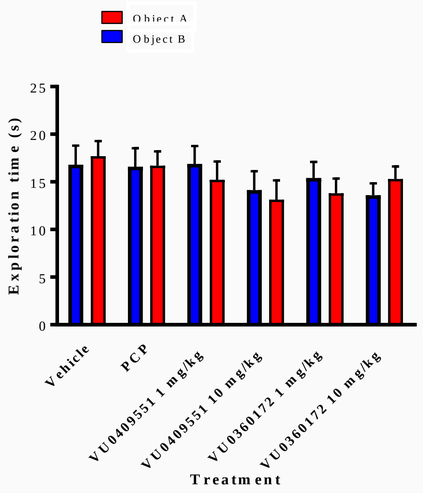


The use of PAMs could add a higher degree of selectivity to mGlu5-mediated signal transduction as compared to orthosteric compounds

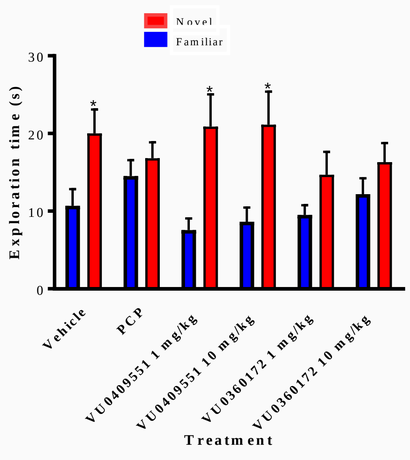
Figure 1.

Results

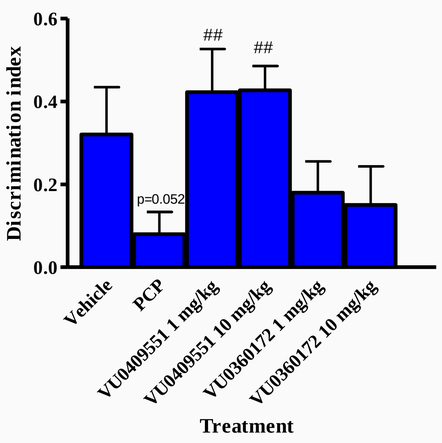
Novel Object Recognition Test
Cohort: 1



- **No difference in time spent exploring object A compared with object B in the acquisition trial.**

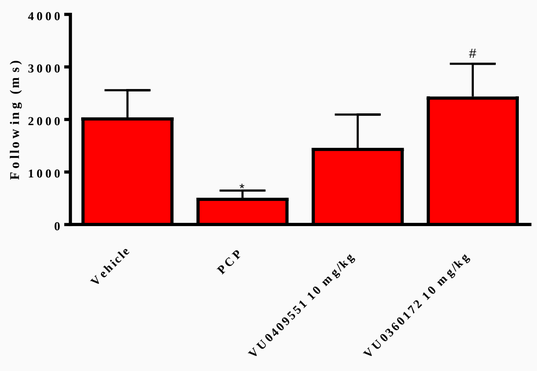


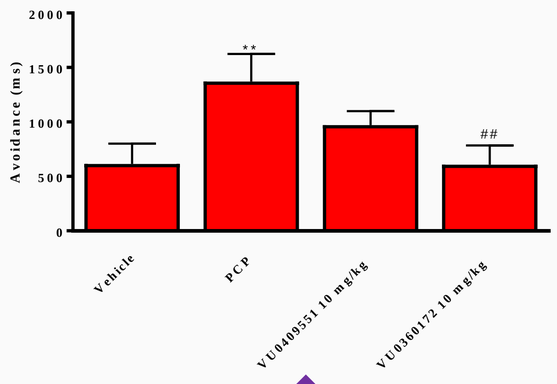
- **Significant increase in time exploring the novel object in the vehicle group.**
- **scPCP-treated rats do not discriminate between novel and familiar objects.**
- **VU0409551 at both doses reversed the scPCP deficit.**
- **VU0360172 failed to significantly reverse the scPCP deficit.**



- **scPCP induces a reduction in the rats ability to discriminate between novel and familiar objects**
- **VU0409551 but not VU0360172 reversed the reduction in DI.**

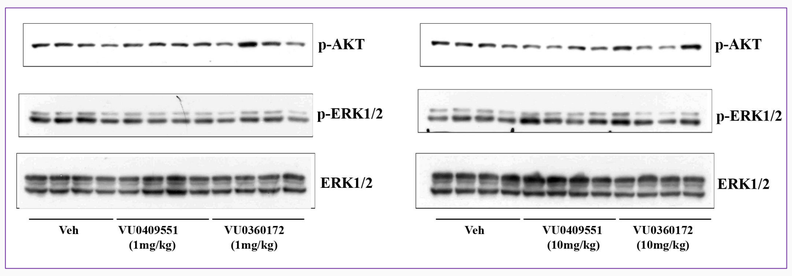
Social Interaction Test
Cohort: 2



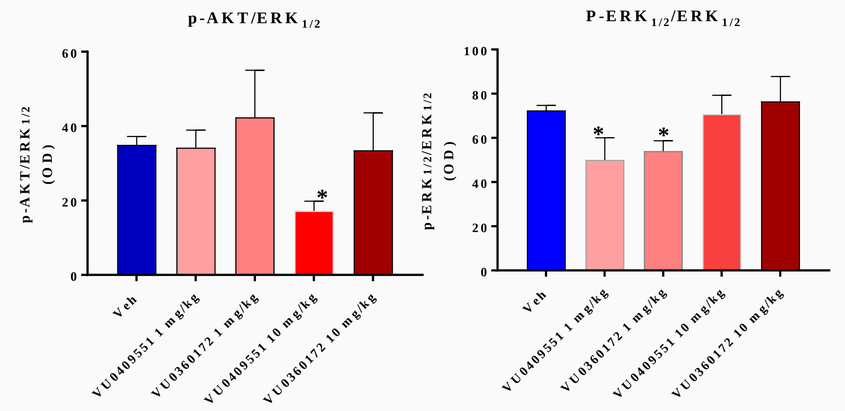


- **Significant decrease in following and significant increase in avoiding in the scPCP group compared to vehicle.**
- **VU0360172 but not VU0409551 significantly reversed the scPCP induced decrease in following and increase in avoidance behaviours.**

mGlu5 receptor-mediated p-AKT and p-ERK1/2 phosphorylation in pre-frontal cortex
Cohort: 1



Densitometric analysis



- **Only VU0409551 (10 mg/kg) significantly decreased p-AKT activation (*p<0.001 vs Veh)**
- **Both VU0409551 and VU0360172 (1 mg/kg) significantly decreased p-ERK1/2 activation (* p<0.05 vs Veh).**

	p-AKT	P-ERK	NOR	SI
VU0409551 1 mg/kg	X	Reduction	Effective	X
VU0409551 10 mg/kg	Reduction	X	Effective	X
VU0360172 1 mg/kg	X	Reduction	X	X
VU0360172 10 mg/kg	X	X	X	Effective

Overview of mGlu5 receptor-mediated p-AKT and p-ERK1/2 phosphorylation in the PFC and behaviour.

Conclusions

- Here we compare for the first time the efficacy of VU0409551 and VU0360172 to restore recognition memory deficits in the scPCP model. We demonstrate efficacy of VU0409551 but not VU0360172.
- Conversely, treatment with VU0360172 but not VU0409551 demonstrated significant effects to improve social behaviour deficits in the scPCP model.
- Efficacy of VU0409551 in NOR was accompanied by a reduction in p-AKT and P-ERK phosphorylation in the PFC, supporting an important role for these signalling pathways in improving cognitive function in psychiatric disorders.
- The role of signalling pathways on the improvements of social behaviour deficits following treatment with VU0360172 require further investigation.