A novel Kv3 ion channel modulator restores cognitive function in an animal model of cognitive impairment in schizophrenia

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Introduction

Schizophrenia is a chronic psychiatric disorder affecting 1% of the population, with a typical onset between the ages of 15 and 35 years. Although positive symptoms of the disorder are reasonably well controlled by current medications, cognitive dysfunction and negative symptoms remain poorly treated. Development of improved treatments with efficacy across the spectrum of symptoms and a lower burden of side effects is therefore of the utmost importance.

The voltage gated ion channel Kv3, mainly located on Parvalbumin (PV) GABAergic interneurons, is closely involved in brain circuitry thought to be affected in schizophrenia. Thus, no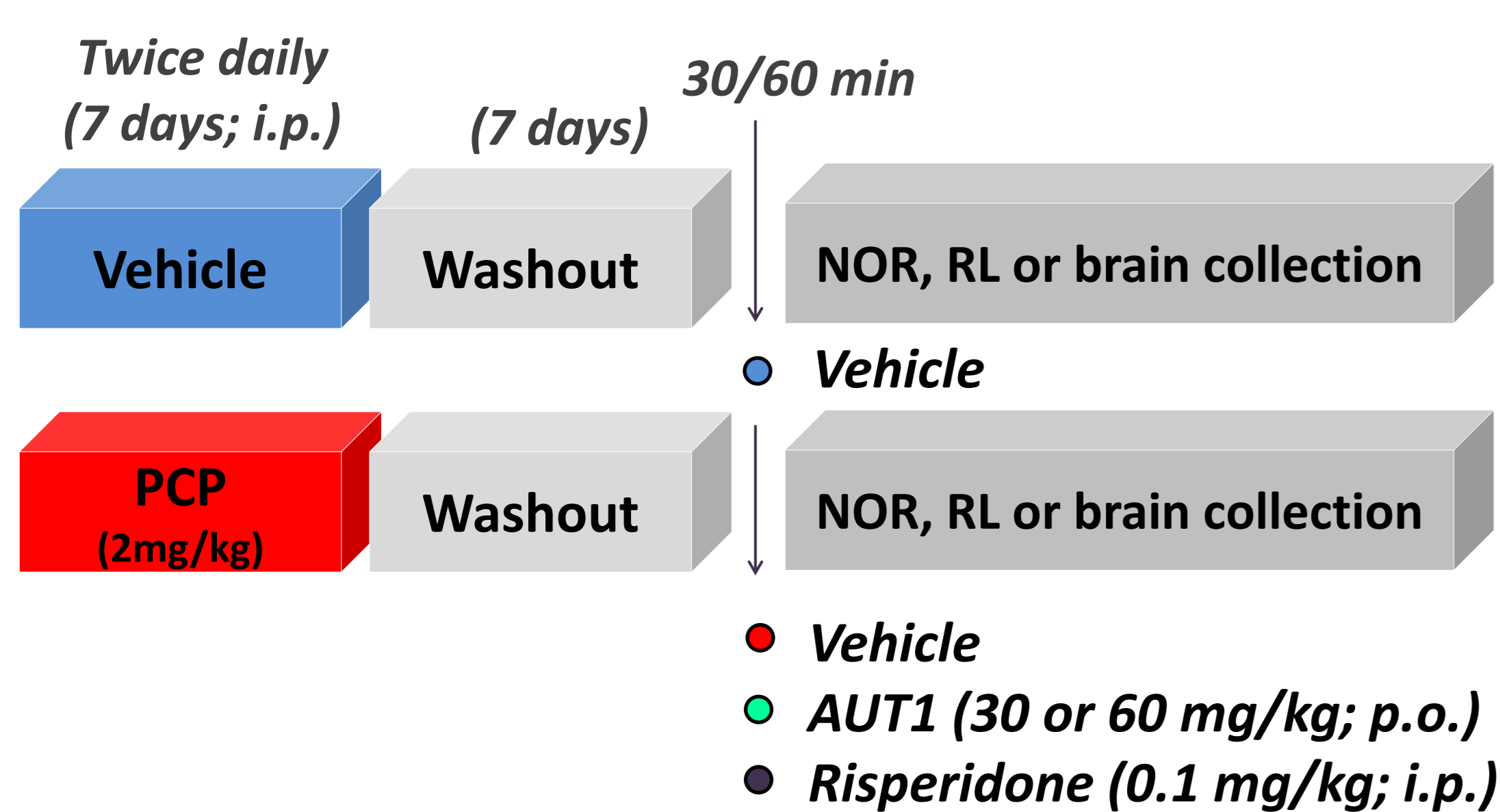vel Kv3 channel modulators may provide an improved therapy, particularly for cognitive deficits and, perhaps, negative symptoms.

In animals, the sub-chronic administration of the NMDA receptor antagonist, Phencyclidine (PCP), has been shown to be particularly relevant to replicate the deficits in a number of cognitive domains affected in schizophrenia[1].
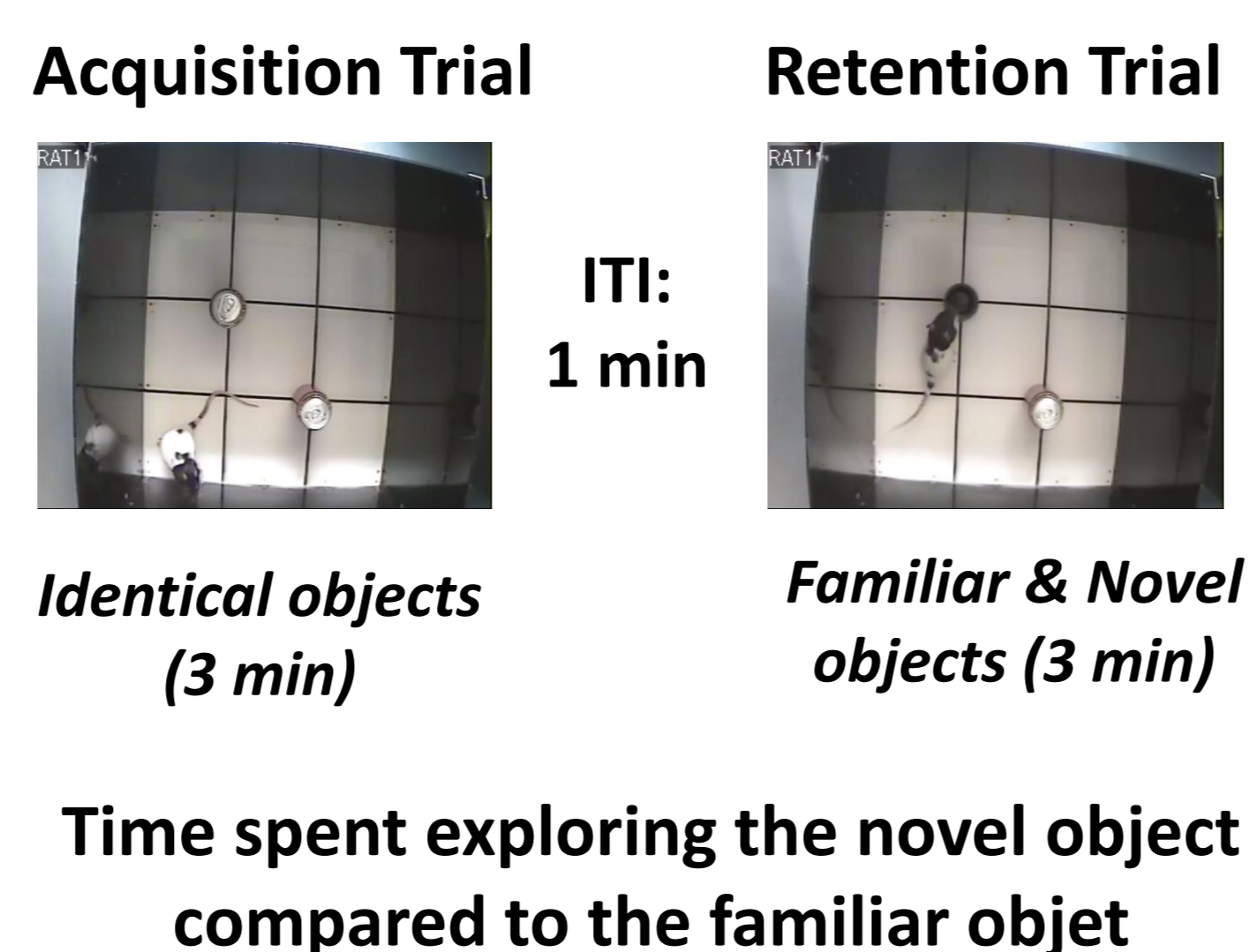
The aim was to assess the **efficacy of a novel and selective Kv3 channel modulator, AUT1, to reverse the cognitive deficits** in **sub-chronic PCP model of schizophrenia**. To better understand the neurobiological mechanisms underlying the PCP effects, the **influence of PCP treatment on PV interneurons and Kv3 channels** has also been investigated.
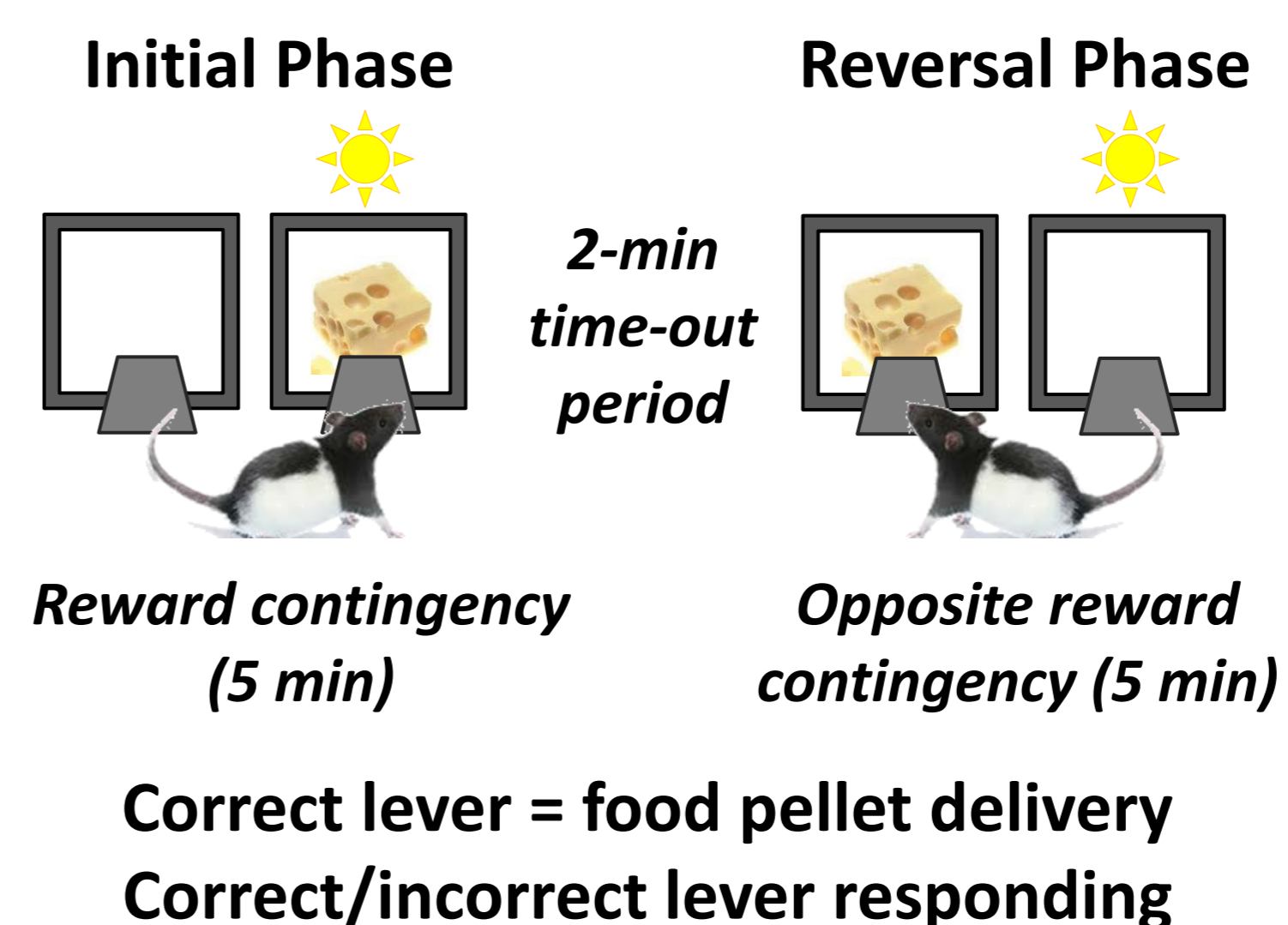
Methods
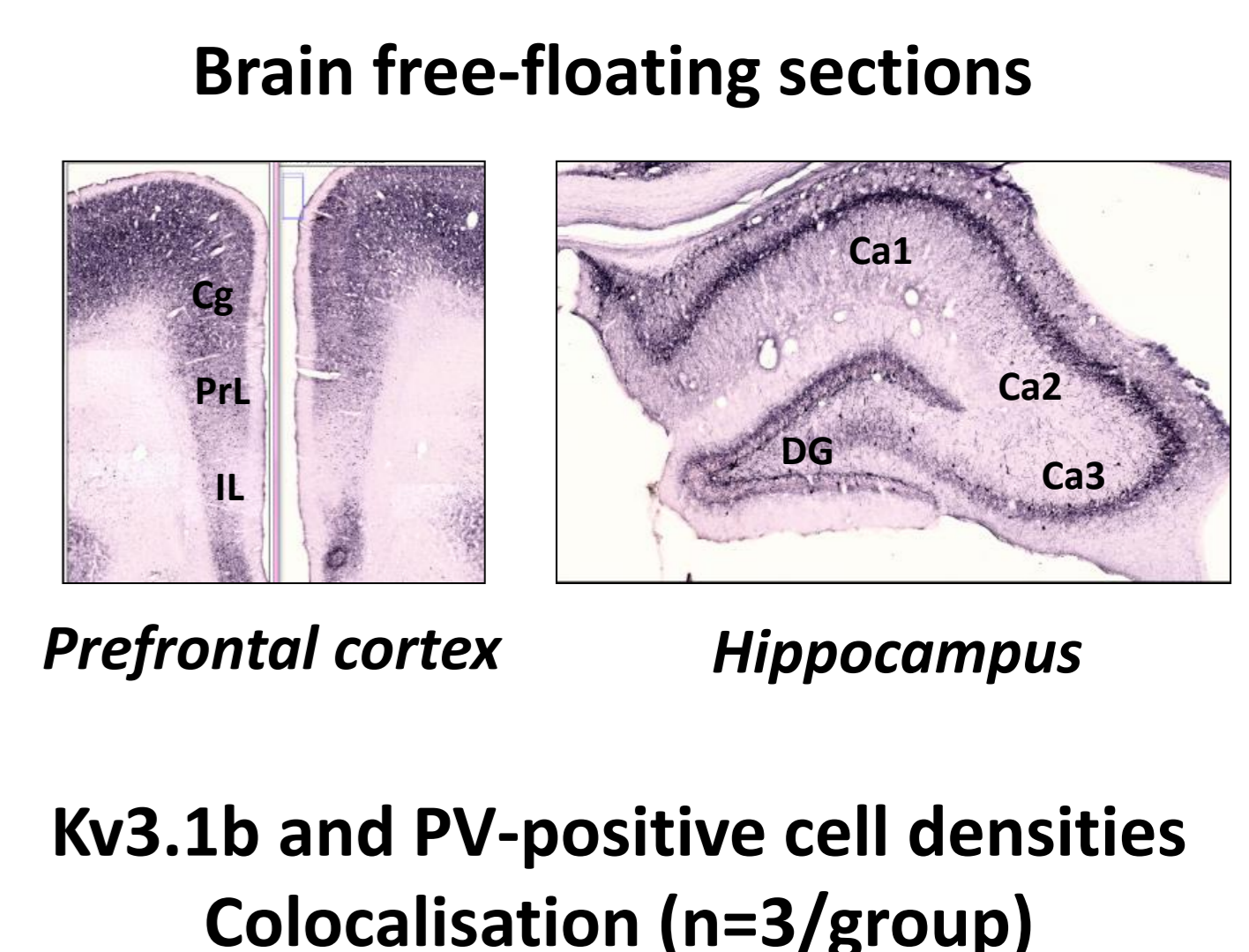

Female Hooded-Lister rats receiving:
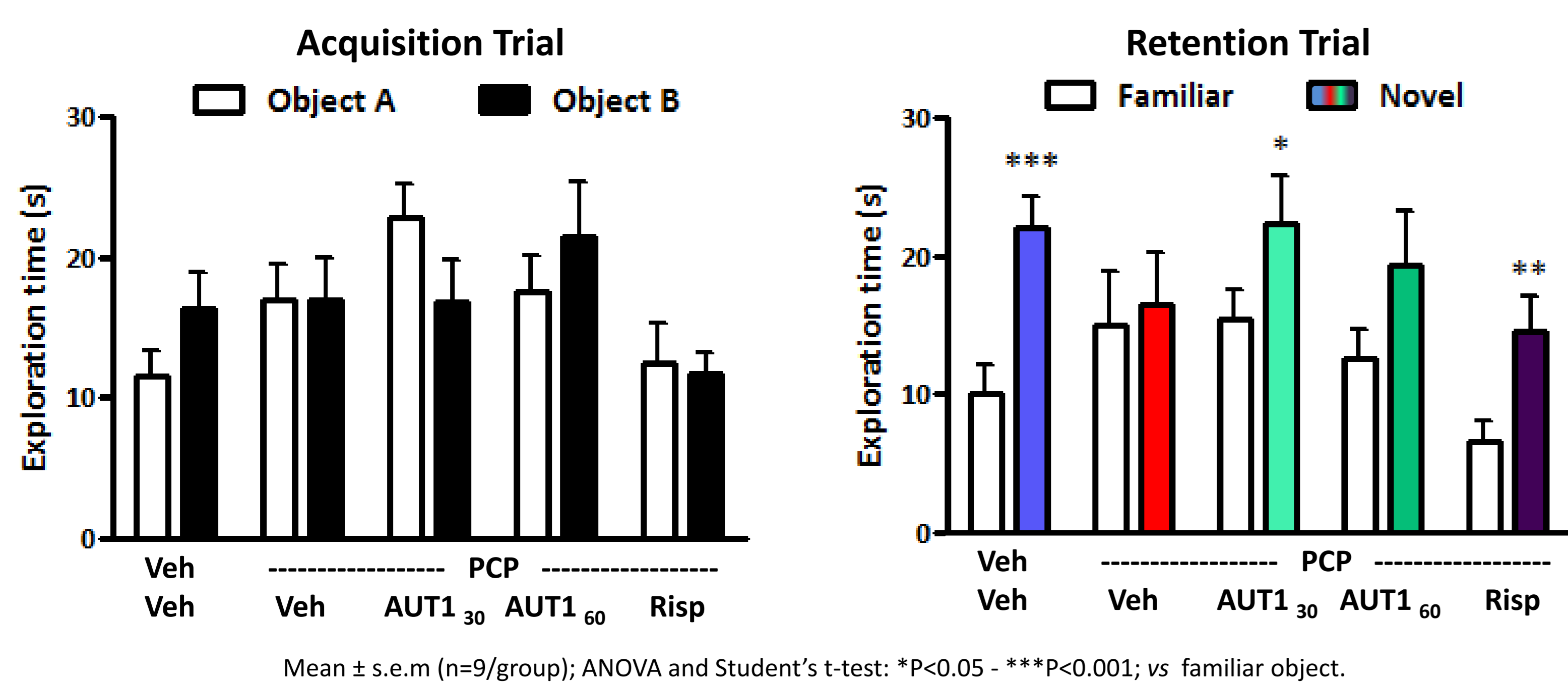
Novel object recognition (NOR; n=50)

Acquisition Trial — *Identical objects (3 min)*
Retention Trial — *Familiar & Novel objects (3 min)*
ITI: 1 min

Time spent exploring the novel object compared to the familiar objet

Reversal learning (RL; n=50)

Initial Phase — *Reward contingency (5 min)*
Reversal Phase — *Opposite reward contingency (5 min)*
2-min time-out period

Correct lever = food pellet delivery
Correct/incorrect lever responding

Immunohistochemistry (n=5 Vehicle and n=5 PCP)

Brain free-floating sections
Prefrontal cortex — *Hippocampus*

Kv3.1b and PV-positive cell densities
Colocalisation (n=3/group)

Results

Novel Object Recognition

Mean ± s.e.m (n=9/group); ANOVA and Student's t-test: *P<0.05 - ***P<0.001; *vs* familiar object.
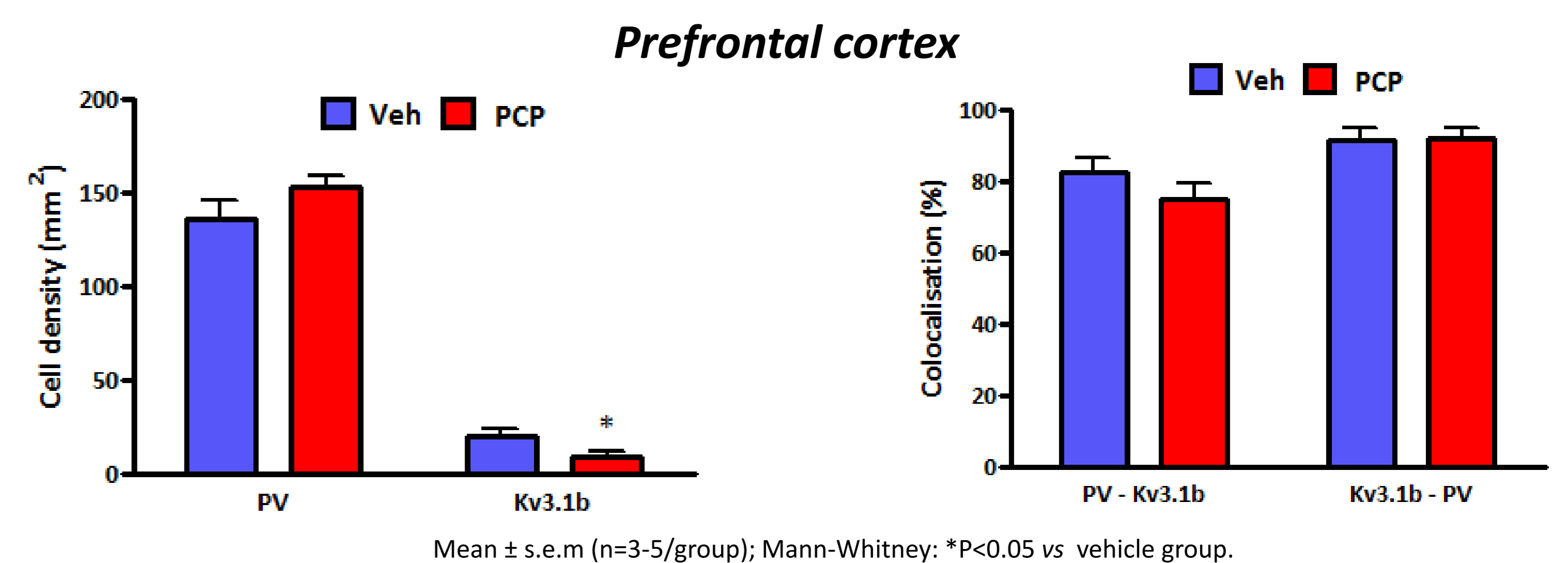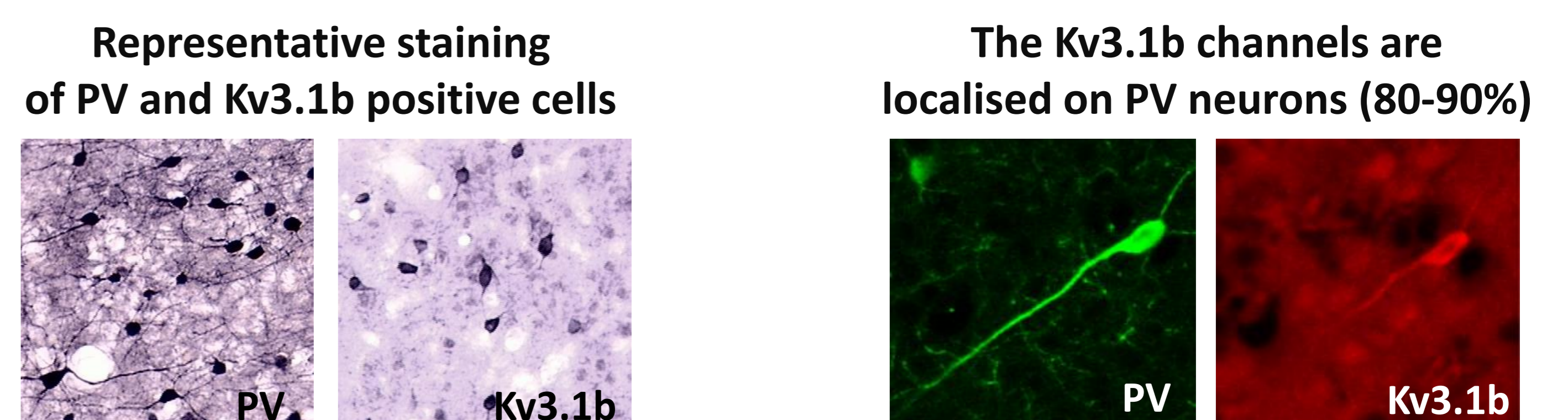
Sub-chronic PCP produced a significant deficit

AUT1 at 30 mg/kg significantly reduced the deficit, as did risperidone

Reversal learning

Mean ± s.e.m (n=9/group); ANOVA and LSD t-test: ***P<0.001; *vs* vehicle group; # P<0.05 - ### P<0.001; *vs* PCP group.

Sub-chronic PCP produced a significant deficit

AUT1 at both doses significantly reduced the deficit, as did risperidone
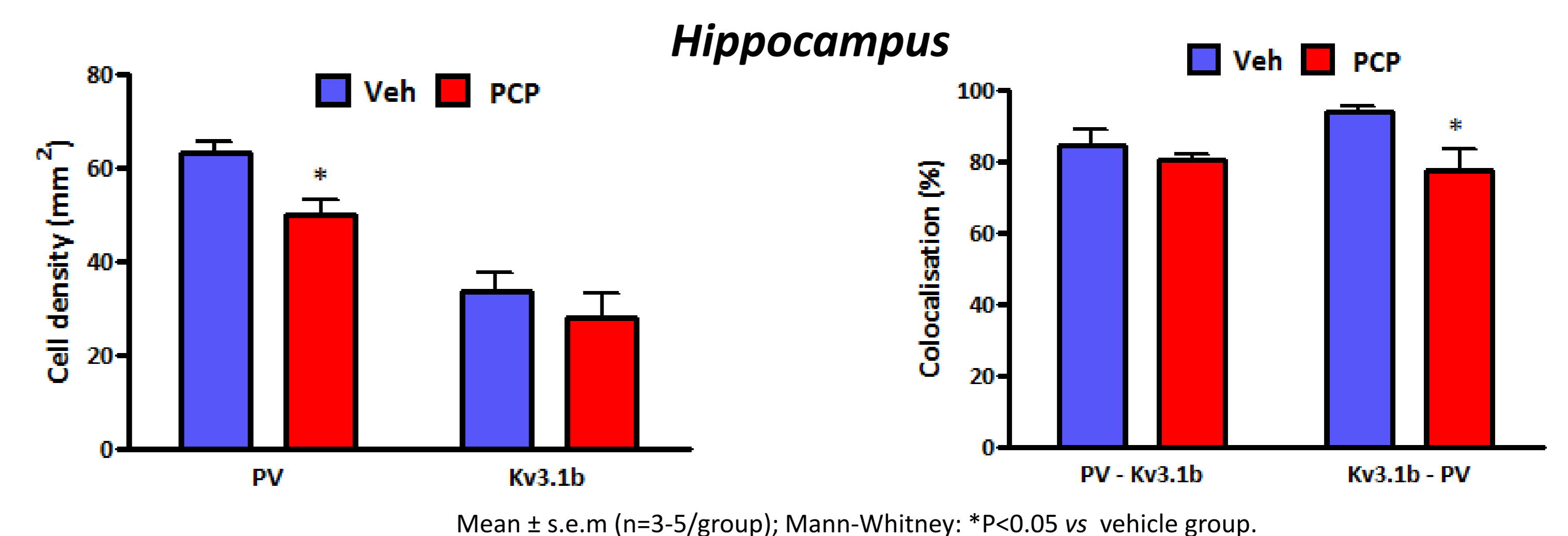
Immunohistochemistry

Representative staining of PV and Kv3.1b positive cells

The Kv3.1b channels are localised on PV neurons (80-90%)

Prefrontal cortex

Mean ± s.e.m (n=3-5/group); Mann-Whitney: *P<0.05 *vs* vehicle group.

Sub-chronic PCP reduced Kv3.1b-positive cell density without affecting % of colocalisation

Hippocampus

Mean ± s.e.m (n=3-5/group); Mann-Whitney: *P<0.05 *vs* vehicle group.

Sub-chronic PCP reduced PV cell density and % of colocalisation

Conclusions

- **AUT1, a novel Kv3 channel modulator, demonstrates efficacy in two cognitive domains (recognition memory and problem solving)**
- **AUT1 alleviates the cognitive deficits in the PCP model in a manner comparable with low dose risperidone**
- **The parvalbumin cell and Kv3-positive cell densities are affected in the PCP model**
- **The modulation of Kv3 channels could be an important target for improving symptomatology of schizophrenia**

1. Neill, JC, Barnes, S, Cook, S, Grayson, B, Idris, NF, McLean, SL, Snigdha S, Rajagopal, L, Harte, MK. (2010) Animal models of cognitive dysfunction and negative symptoms of schizophrenia: focus on NMDAR receptor antagonism. Pharmacology and Therapeutics, 128(3), 419-432.