

Intra-IOFC 5-HT2C-specific hM3Dq and touchscreen reversal learning

Marie Dupraz
Sebastian Axelsson
Annika Thomsen
Doaa Hassan
AA Berthiaume

Systemic and intra-OFC 5-HT_{2C} antagonism

Psychopharmacology
DOI 10.1007/s00213-015-3963-5

ORIGINAL INVESTIGATION

J. Alsiö^{1,2,3} · S. R. O. Nilsson^{1,2} · F. Gastambide⁴ · R. A. H. Wang^{1,2} ·
S. A. Dam^{1,2} · A. C. Mar^{1,2} · M. Tricklebank⁴ · T. W. Robbins^{1,2}

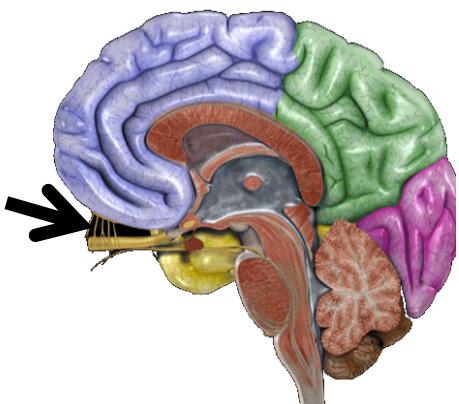
The role of 5-HT_{2C} receptors in touchscreen visual reversal learning in the rat: a cross-site study

5-HT_{2C}Rs: Predominantly on PFC interneurons (Cunningham et al.)

Constitutive Gq activity (Herrick-Davies et al 1999)

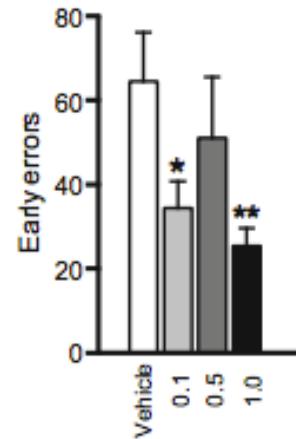
≈ 24 isoforms (Hackler et al. 2006).

OFC
Decreased activity at the 5-HT_{2C}R appears to increase sensitivity of pyramidal OFC cells (Reuter et al., 2000)

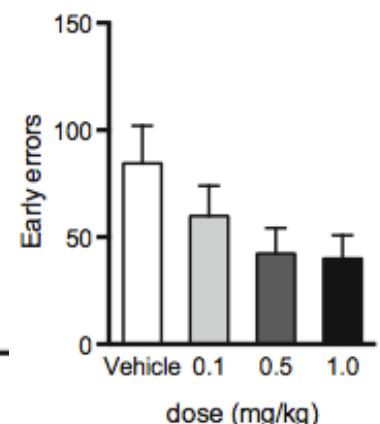


SYSTEMIC 5-HT_{2C} ANTAGONIST

3-choice reversal

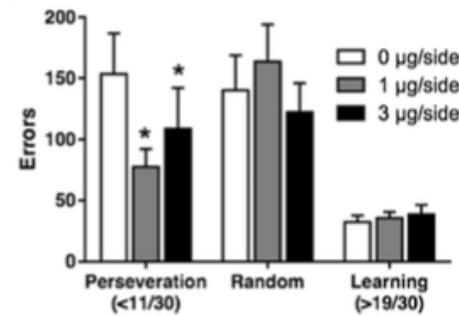


2-choice reversal



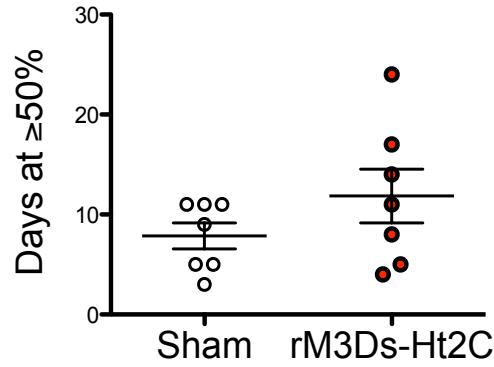
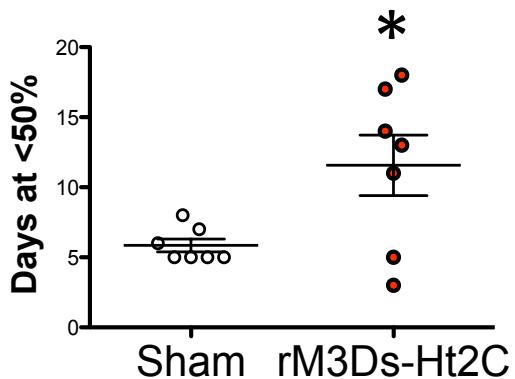
Reversal 1

INTRA-OFC 5-HT_{2C} ANTAGONIST



rM3Ds-HT2C IOFC and systemic CNO (3 mg/kg)

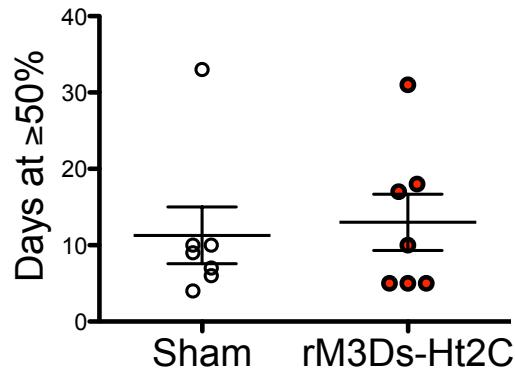
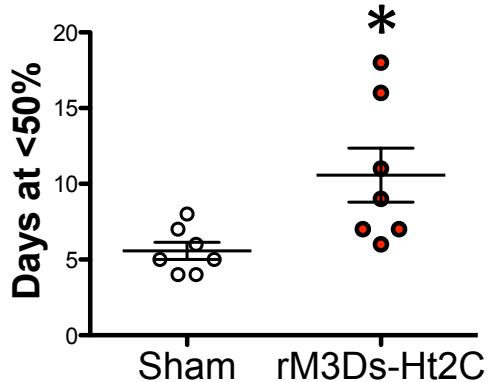
Reversal 1



Control sham group:
2C-cre NEG + rM3Ds

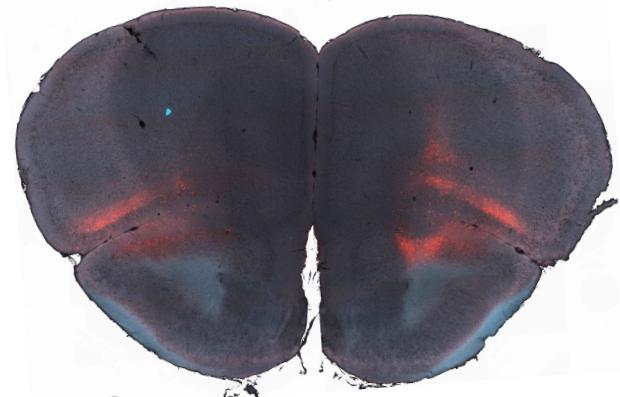
Experimental group:
2C-cre POS + rM3Ds

REVERSAL 2



CNO given throughout

! No vehicle control – could be effect of DREADD expression



SURGERY

6×10^{12} AAV2 hM3Dq
0.5 μ l IOFC

2C-cre NEG N = 17

2C-cre POS N= 15

Pre-training

VISUAL DISCRIMINATION (CNO FREE)



REVERSAL 1 (CNO FREE)



RETENTION (4 days) (CNO FREE)

Vehicle



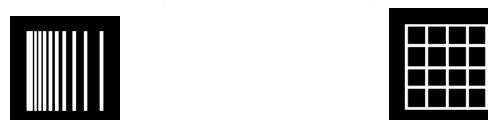
Vehicle (last 2 days)



Vehicle

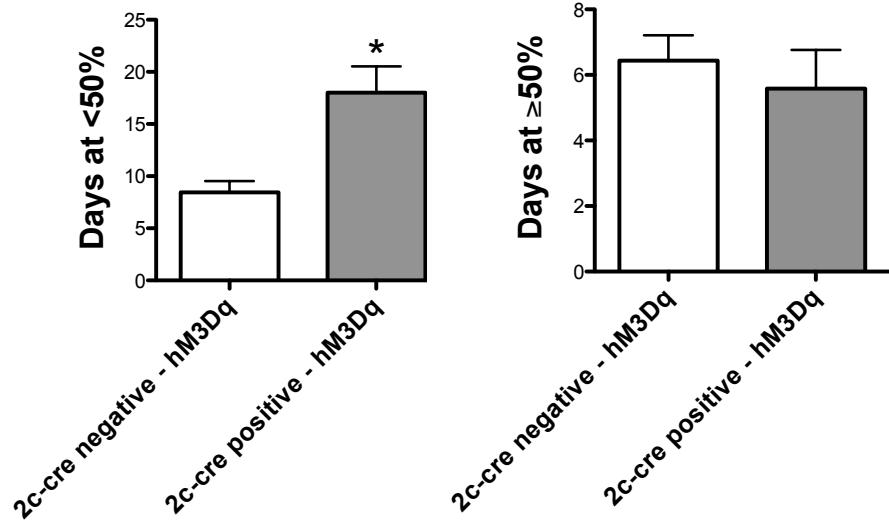
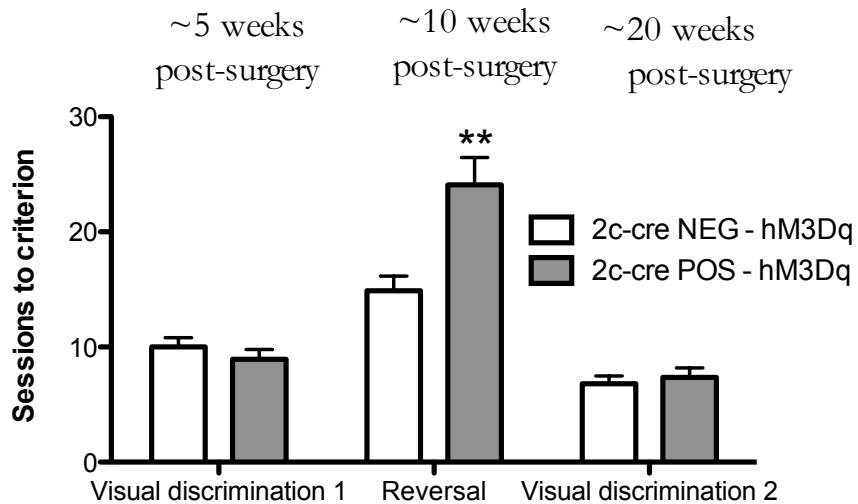


VISUAL DISCRIMINATION 2 (CNO FREE)



OFC Gq in HT2C-cre pos. and neg. animals (0.5 μ l, AAV2, 6×10^{12})

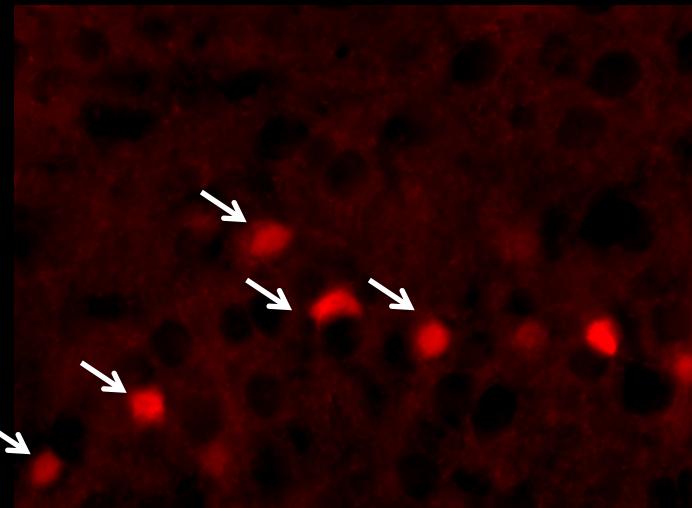
NO CNO IN VD's OR REV



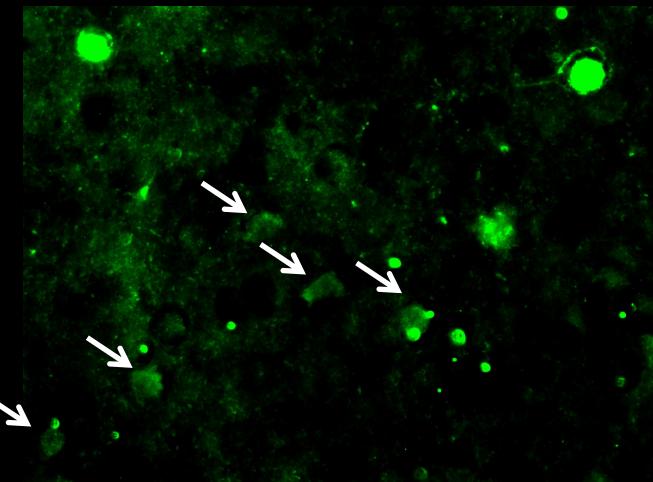
2c-cre positive hM3Dq animals show reversal-specific impairment
Deficit specific to early reversal

PV+ / 2C YFP overlap in control animal

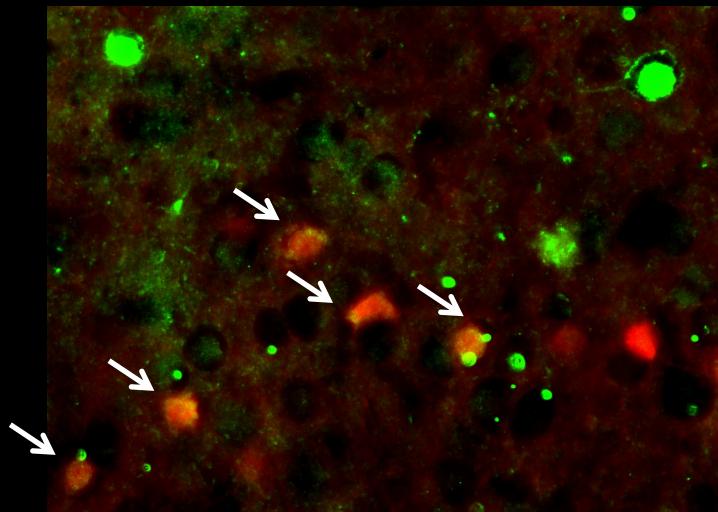
5-HT2C YFP



PV

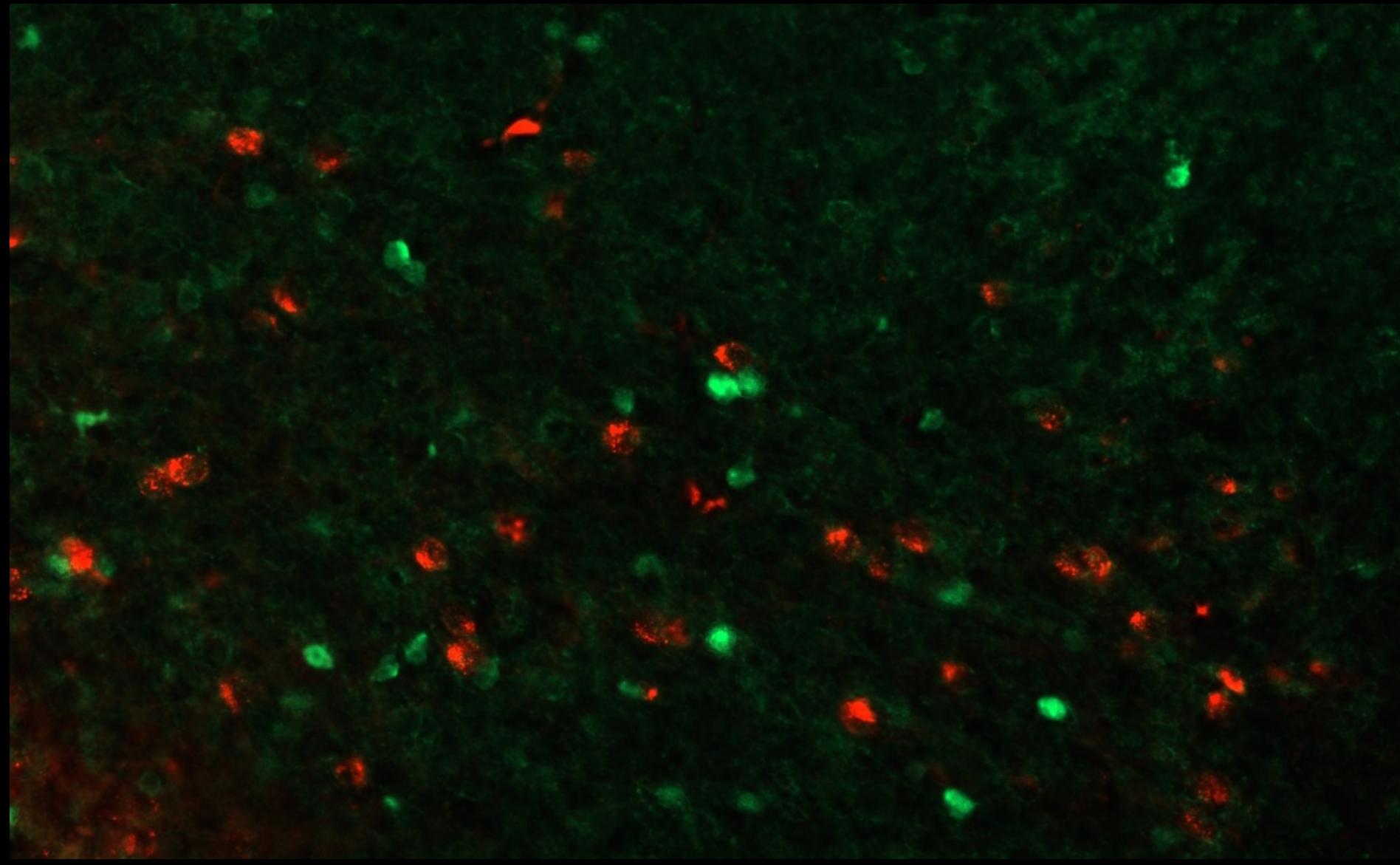


5-HT2C YFP + PV



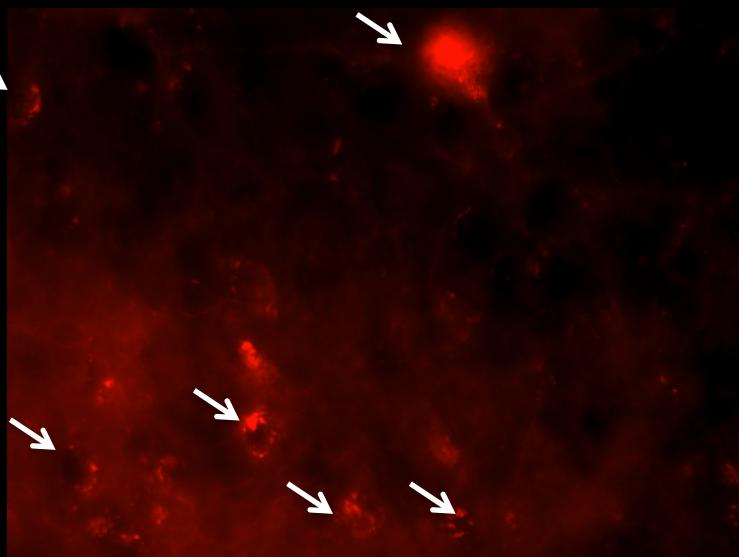
5-HT2C and PV colocalise

Little or no 5-HT2C YFP / PV overlap after hMD3q intra-IOFC in 2C-cre POS mice

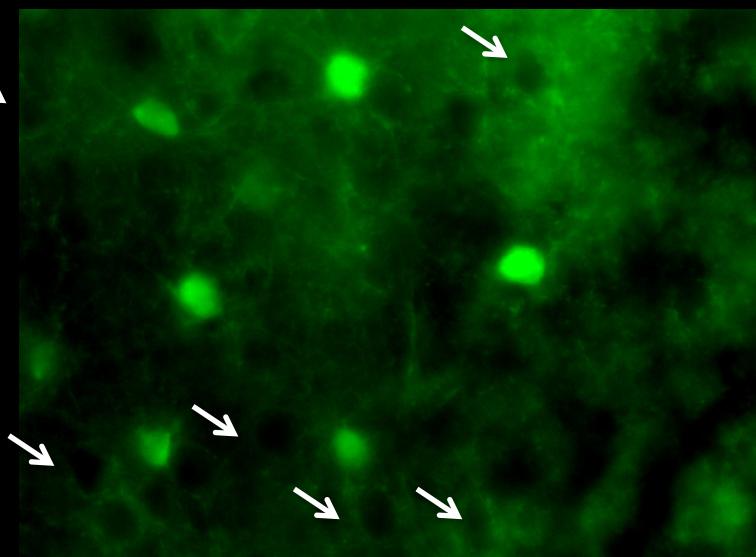


No 5-HT2C YFP + PV overlap in Gq animals

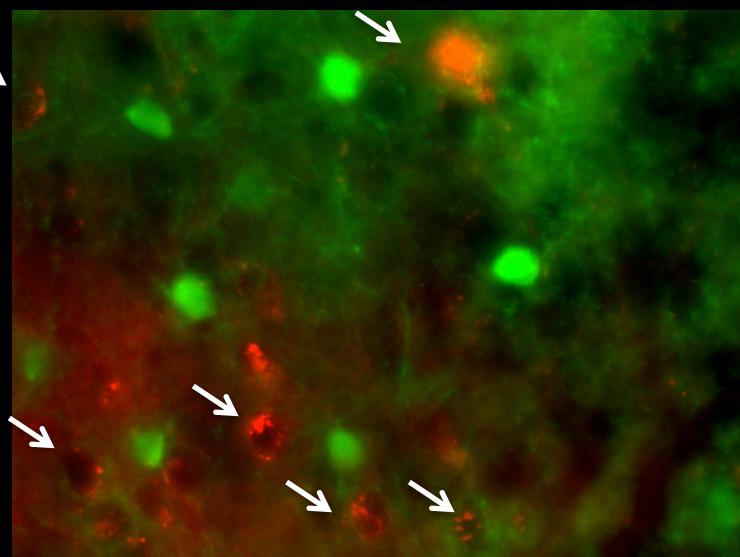
5-HT2C YFP



PV



5-HT2C YFP + PV



Ephys results so far and what's next

- (i) mCherry / hM3Dq infected cells in 2c-cre positive animals **not** healthy – so far unable to patch a single cell.
- (ii) Non-infected IOFC cells in 2c-cre positive animals appear healthy

NEXT STEPS

- (i) Find lower AAV2 / hM3Dq volume and titer that does leave PV intact
(PILOT SURGERIES DONE)
- (ii) New batch of 40 2C-cre POS/NEG animals trained and ready for surgery

Some comments

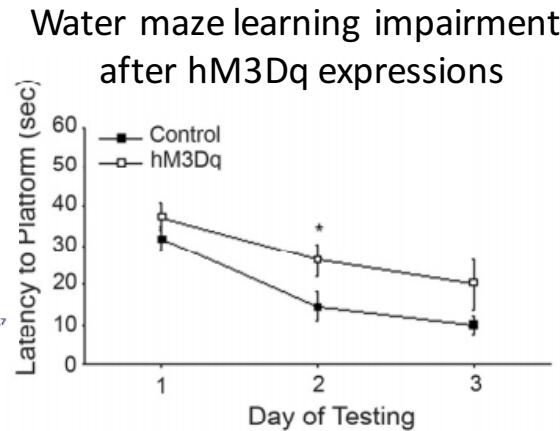
Yau and McNally 2005
Saksaki et al. 2011

2×10^{12} particles/mL
 5.7×10^{12} particles/mL

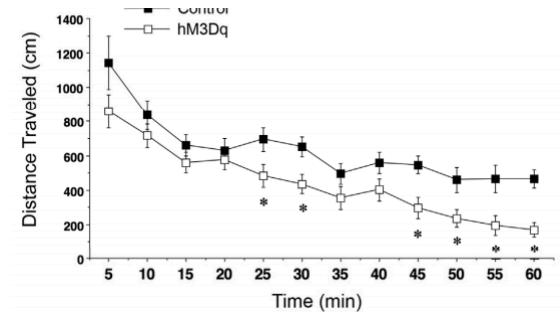
Neuron
Neurotechnique

Remote Control of Neuronal Activity in Transgenic Mice Expressing Evolved G Protein-Coupled Receptors

Georgia M. Alexander,^{10,12} Sarah C. Rogan,^{2,12} Athir I. Abbas,¹¹ Blaine N. Armbruster,² Ying Pei,² John A. Allen,^{2,7}
Randal J. Nonneman,⁷ John Hartmann,¹ Sheryl S. Moy,^{3,7} Miguel A. Nicolelis,¹⁰ James O. McNamara,^{10,*}
and Bryan L. Roth^{2,3,4,5,6,7,8,9,*}



Hypoactivity
after hM3Dq expressions



Original hM3Dq paper:
Expression in mouse cortical principal cells **IS NOT** behaviourally inert

Many /most studies do not have behavioural/ephys controls for genotype/DREADD and CNO