Effects of systemic and intra-OFC 5-HT$_{2C}$R antagonism on visual reversal learning in the rat

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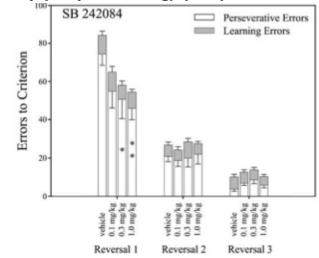
SB242084 and reversal learning

5-HT$_{2C}$R antagonism is a component of most atypical antipsychotics.

Decreased activity at the 5-HT$_{2C}$R appears to increases sensitivity in OFC (Reuter et al., 2000) and elevate dialysate dopamine in the accumbens (Millan et al., 1999).

Vasileios Boulougouris*,[1], Jeffrey C Glennon[2,3] and Trevor W Robbins[1]
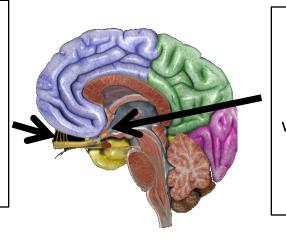
Vasileios Boulougouris and Trevor W. Robbins

OFC
Increased activity associated with improved learning

NAc
Increased dopamine associated with impaired learning

SB242084 and reversal learning

★ 3-stimulus VD and reversal and systemic SB242084 (UCAM, Lilly)

★ OFC-specific SB242084 infusions in 2-stimulus serial reversal learning (UCAM)

SB242084 and 3-stim VD and reversal

⭐ More difficult than standard 2-stim reversal learning

⭐ Better discernment of a perseverative response strategy to the previous S+
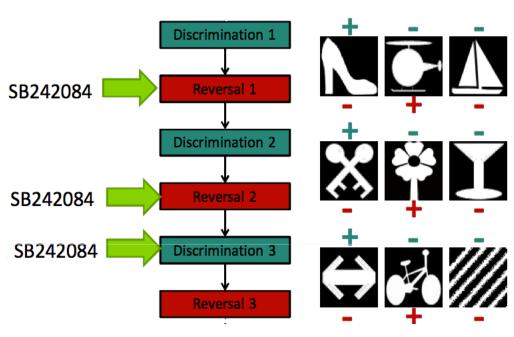
⭐ Responses toward the continuously non-rewarded S- measures use of random response strategy

⭐ Effect of drug analysed by three- or two-way between-subjects ANOVAs including the phases where SB242084 was administered. Reversal 3 analysed by one-way ANOVAs.

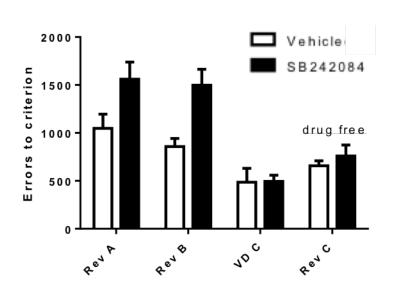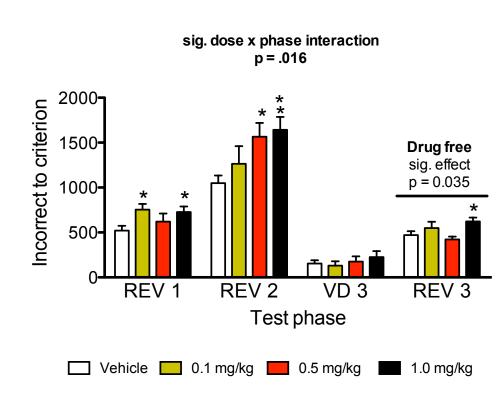| Lilly: | 0.1, 0.5, 1.0 mg/kg |
| Cambridge: | 1.0 mg/kg |

cf. Jentsch et al. 2002 Neuropsychopharm

Criterion: 9 correct / 10 trials x 2 (rolling trial count)

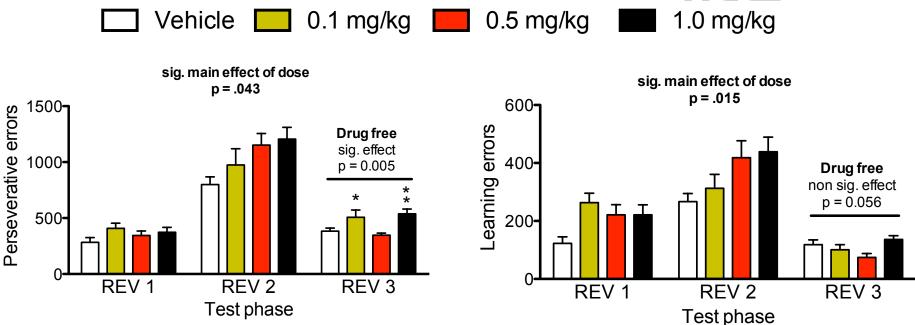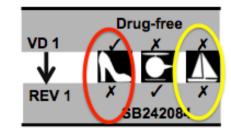# SB242084: 3-stim reversal learning (Lilly)

UCAM

LILLY

SB242084 increases trials and incorrect responses to criterion in reversal learning without affecting VD-performance
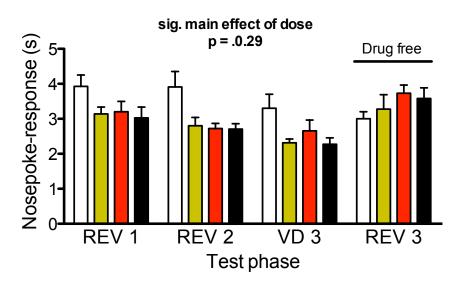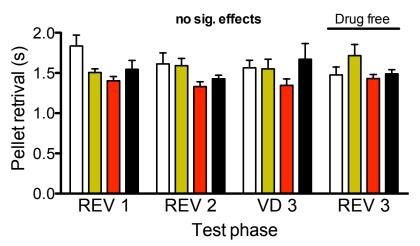
SB242084: 3-stim reversal learning (Lilly)

SB242084 increases both 'learning' and 'perseverative'-errors

SB242084: 3-stim reversal learning (Lilly)

newmeds

☐ Vehicle   ▨ 0.1 mg/kg   ▮ 0.5 mg/kg   ■ 1.0 mg/kg

sig. main effect of dose
p = .0.29

Drug free

Nosepoke-response (s)

REV 1   REV 2   VD 3   REV 3

Test phase

no sig. effects

Drug free

Pellet retrival (s)

REV 1   REV 2   VD 3   REV 3

Test phase
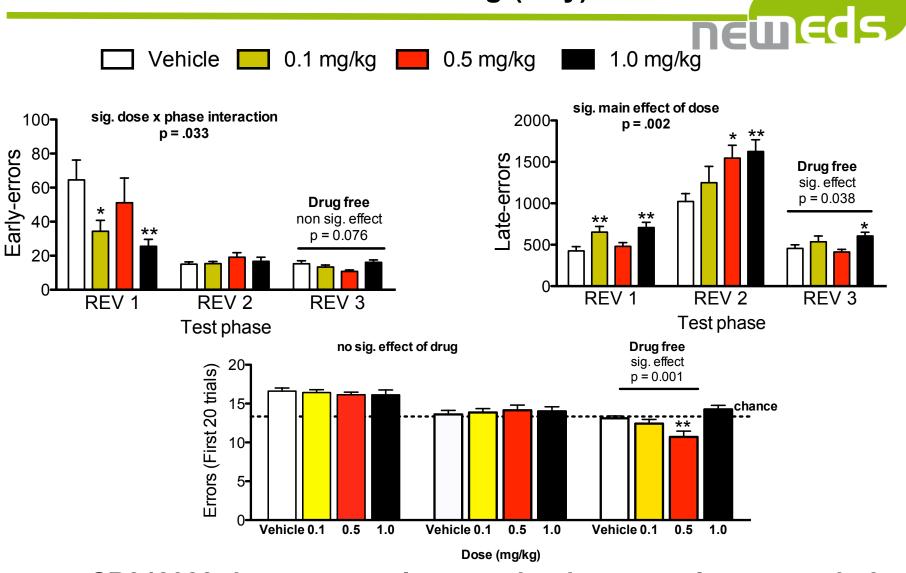
SB242084 decreases response latencies

SB242084: 3-stim reversal learning (Lilly)

newmeds

Vehicle ▮ 0.1 mg/kg ▮ 0.5 mg/kg ▮ 1.0 mg/kg

sig. dose x phase interaction
p = .033

Early-errors

Drug free
non sig. effect
p = 0.076

REV 1   REV 2   REV 3
Test phase

sig. main effect of dose
p = .002

Late-errors

*   **
Drug free
sig. effect
p = 0.038

REV 1   REV 2   REV 3
Test phase

no sig. effect of drug

Errors (First 20 trials)

Drug free
sig. effect
p = 0.001

chance

Vehicle 0.1 0.5 1.0   Vehicle 0.1 0.5 1.0   Vehicle 0.1 0.5 1.0
Dose (mg/kg)

SB242082 decreases early-errors but increases late-errors in 3-stim reversal learning

2-stim task suitable for infusion study (UCAM - Alsiö)

newmeds

★ Standard reversal tasks unsuitable for infusion study

★ Serial 2-choice reversal task with robust perseverative responding and fast reversals.

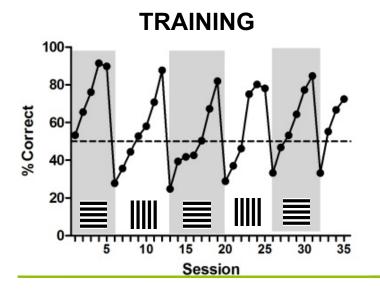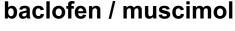★ Optimal performance achieved at criterion: 24 / 30 correct (running trial count)
   Perseverative phase: < 11 / 30 correct
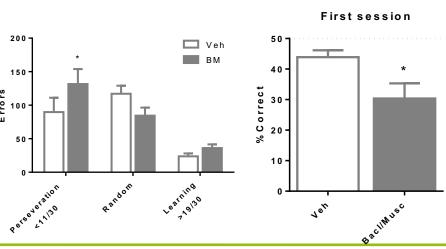   *Learning phase:*   > 19 / 30 correct
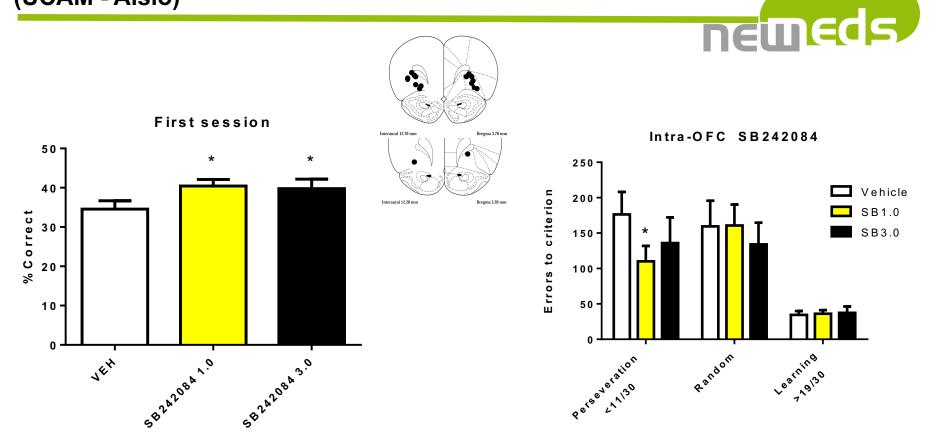   *Random phase:*   ≥ 11 & ≤ 19 / 30 correct

★ OFC-dependent early perseverative-phase - validated by baclofen / muscimol infusions

TRAINING

baclofen / muscimol

Reduced early-errors re-produced by OFC SB242084-infusion (UCAM - Alsiö)
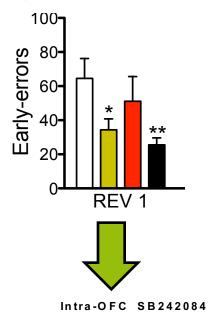

First session

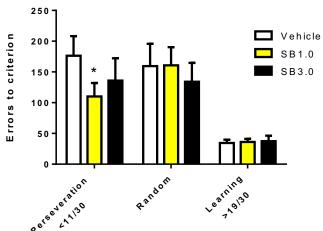*Within-subjects, drug- and stimulus-order counterbalanced*

OFC SB242084-infusion improves performance early in reversal without affecting learning late in reversal
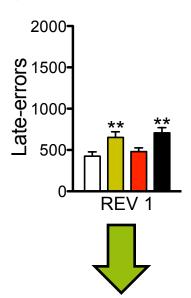
ONGOING: SB242084, late errors, and VTA?

Conclusions

★ **Systemic 5-HT$_{2C}$R antagonism improves early learning but impairs late-learning and overall reversal learning.**

★ **No effect of SB242084 on 3-stim discrimination learning**

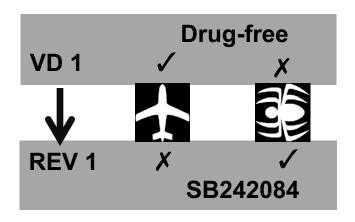★ **SB242084-induced early improvement in reversal learning mediated by the OFC**
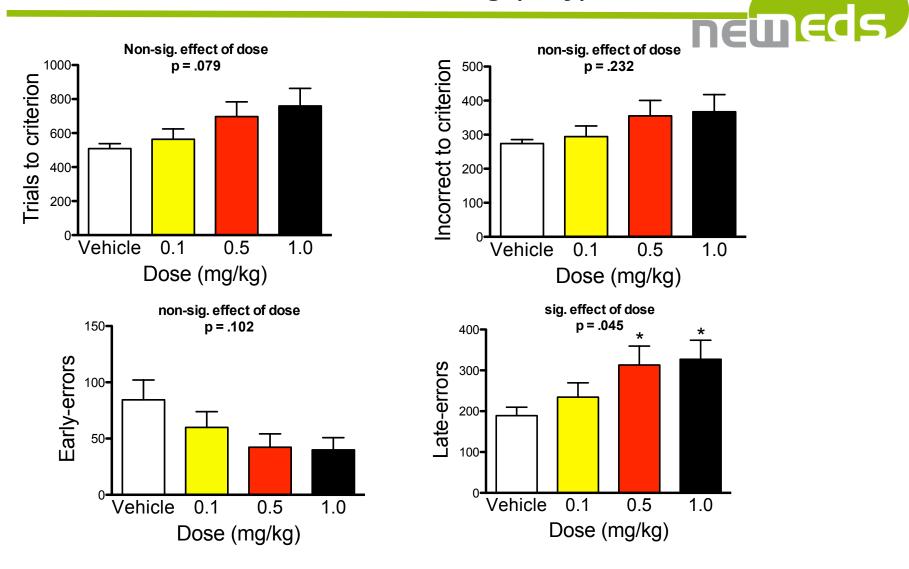
SB242084 and 2-stim reversal learning

Lilly: 0.1, 0.5, 1.0 mg/kg

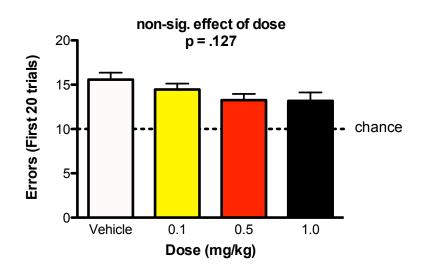**Criterion: 2 x ≥ 9 /10 correct (rolling trial count)**

Early errors : < 5 correct / 10 trials x 2
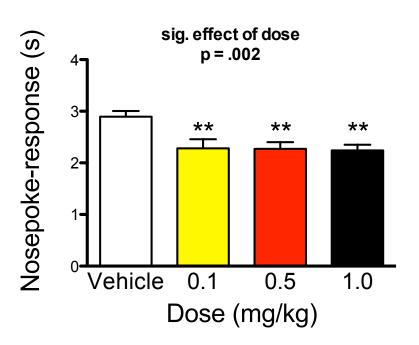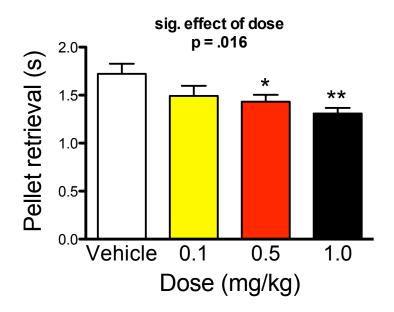**Late errors   : ≥ 5 correct / 10 trials x 2**

analysed by one-way ANOVAs

SB242084: 2-stim reversal learning (Lilly)

Trend towards decreased early-errors but increased late-errors in 2-stim reversal learning

SB242084: 2-stim reversal learning (Lilly)

SB242082 decreases both retrieval latencies and nosepoke response latencies