Pharmacological and chemogenetic investigations of 5-HT$_{2C}$ receptor function in rodent touchscreen visual reversal learning

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BACKGROUND

Reversal learning deficits are observed in psychiatric disorders such as schizophrenia and obsessive-compulsive disorder and implicate neural circuitry including the orbitofrontal cortex (OFC) and activity at 5-HT$_{2C}$ receptors (5-HT$_{2C}$R) in this area. In the current experiments, we developed a novel battery of touchscreen reversal learning tasks and used pharmacological and chemogenetic manipulations to assess the role of 5-HT$_{2C}$R activity in reversal learning in rats and mice.

METHODS

Experiment 1 assessed effects of systemic SB242084 in 2-stimulus reversal learning in the rat.

Experiment 2 investigated effects of systemic SB242084 in 3-stimulus reversal learning in the rat.

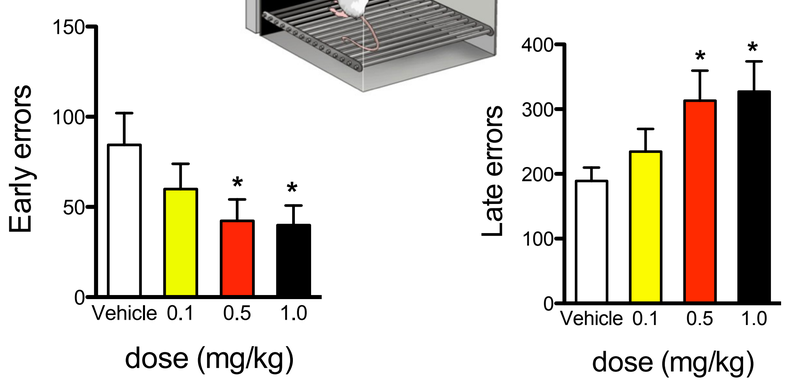
Experiment 3 assessed effects intra-OFC baclofene/muscimol infusion on a novel serial visual reversal task in the rat.

Experiment 4 assessed effects intra-OFC SB242084 infusion on serial visual reversal task in the rat.

Experiment 5 assessed effects intra-OFC rM3DS-infusion in 5-HT2C-Cre positive and negative mice in 2-stimulus reversal learning

Systemic 5-HT$_{2C}$R antagonism

2-choice reversal learning

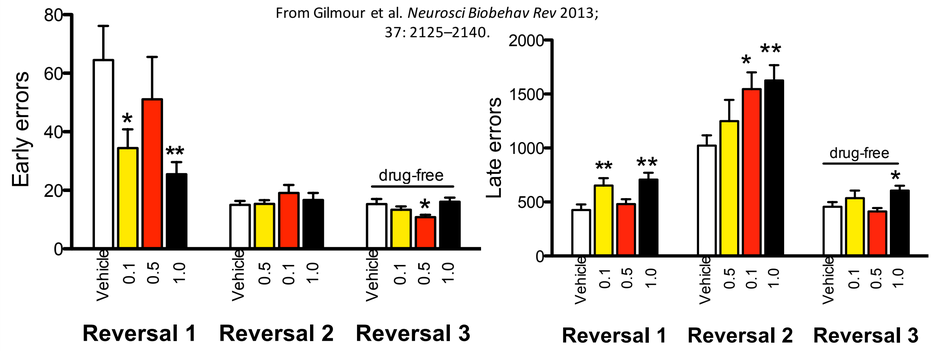


★ **EXPERIMENT 1: Systemic SB242084 improved early learning and impaired late learning in the 2-stimulus task**

Systemic 5-HT$_{2C}$R antagonism

3-choice reversal learning

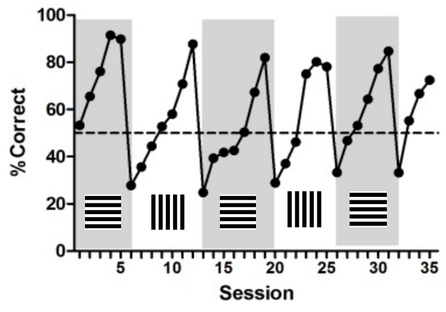
From Gilmour et al. *Neurosci Biobehav Rev* 2013; 37: 2125–2140.

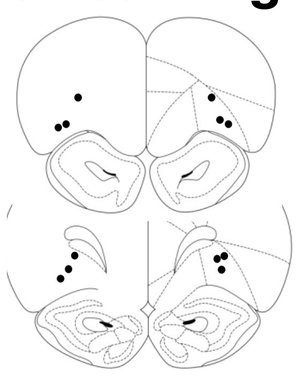


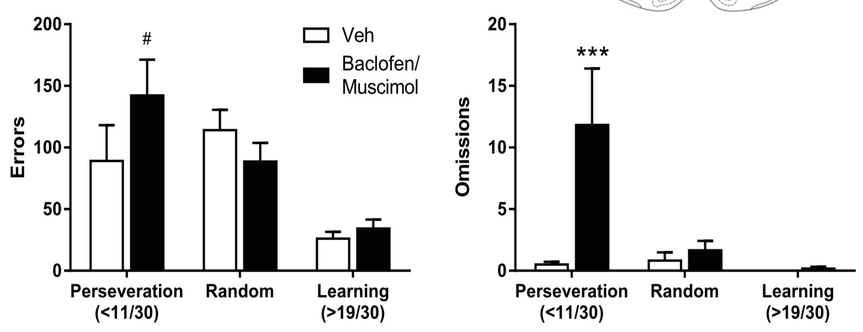
★ **EXPERIMENT 2: Systemic SB242084 improved early learning and impaired late learning in the 3-stimulus task. Effects were observed in labs of both academic and industrial collaborators**

OFC inactivation

2-choice serial reversal learning



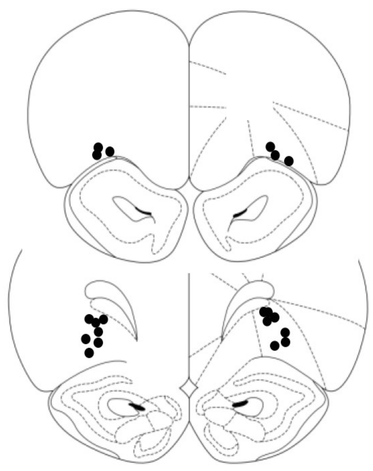


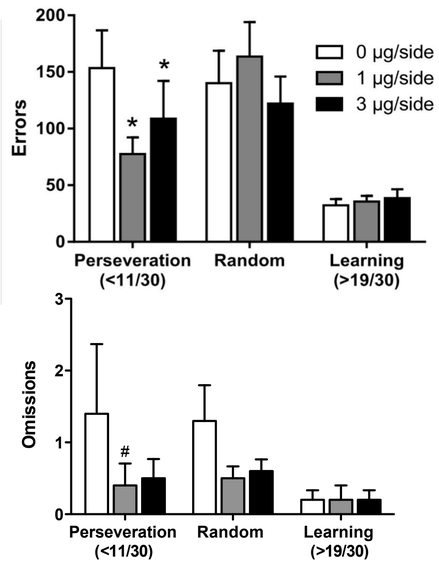


★ **EXPERIMENT 3: Intra-OFC baclofen / muscimol impaired early learning without affecting late learning in the 2-stimulus serial reversal task**

Intra-OFC 5-HT$_{2C}$R antagonism

2-choice serial reversal learning

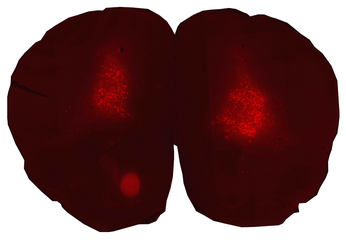


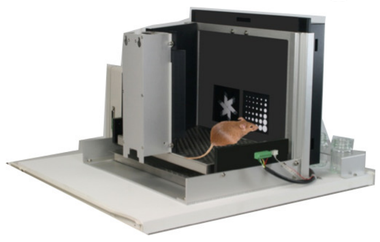


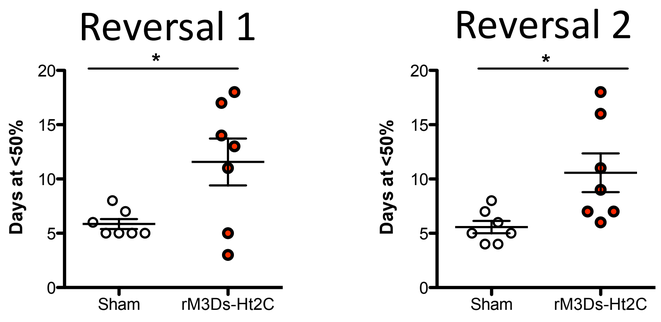
★ **EXPERIMENT 4: Intra-OFC SB242084 infusion improved early learning without affecting late learning in the 2-stimulus serial reversal task**

Intra-OFC rM3Ds / 5-HT2C-Cre

2-choice reversal learning







★ **EXPERIMENT 5: Systemic clozapine-N-oxide (3 mg/kg, i.p.) impaired early reversal learning without affecting late reversal learning in intra-OFC rM3Ds treated 5-HT2C Cre-positive mice.**

CONCLUSIONS

We used pharmacological (systemic and intra-OFC) and chemogenetic (intra-OFC rM3Ds infusion/ HT2CCre mice) manipulations to show that activity at the OFC 5-HT$_{2C}$Rs counteracts maladaptive perseverative responding in a novel, touch-screen controlled, visual reversal learning task for rodents. Normal performance on the reversal task was also shown to depend on OFC function, following its muscimol-induced inactivation. These data on the role of 5HT$_{2C}$Rs extend earlier evidence that OFC 5-HT plays an important role in cognitive flexibility (e.g., Clarke et al. Science 2004; 304: 878–880), possibly relevant to human OCD. Systemic treatment with the 5-HT$_{2C}$R antagonist additionally impaired late reversal learning (though without impairing discrimination learning), an effect of interference presumably mediated at sites other than the OFC.

ACKNOWLEDGEMENTS

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