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

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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 (systemic and intra-OFC) and chemogenetic (intra-OFC rM3Ds infusion/ HT2C-Cre mice) manipulations to show that activity at the OFC 5-HT_{2C}Rs affect early perseverative-like reversal learning performance in rodents.

In Experiment 1-2, we show that systemic 5-HT_{2C}R antagonism through SB242084 dose-dependently decrease early errors but increase late errors in both in 2-choice and 3-choice reversal learning. SB242084 did not affect visual discrimination learning. The effects were replicated in the labs of both industrial (Eli Lilly) and academic (Cambridge University) partners. In Experiment 3, we validate a novel touchscreen serial visual reversal task as suitable for neuropharmacological microinfusion studies by showing that baclofen/muscimol-induced OFC inactivation impairs early but not late learning in this task. In Experiment 4, intra-OFC SB242084 infusions reduced early errors without affecting late errors in this serial visual reversal task. In Experiment 5, we employed 5-HT2C-Cre mice to direct transgenic expression of Gs-coupled engineered receptors (rM3Ds) to 5-HT_{2C}R-containing cells in the OFC. Systemic injection of 3 mg/kg clozapine-N-oxide during the reversal phase impaired

performance in rM3Ds-treated Cre-positive mice during early reversal learning without affecting late reversal learning.

In sum, using novel touchscreen visual reversal learning paradigms, we show that OFC 5-HT_{2C}R antagonism and activation of OFC 5-HT_{2C}R-containing cells decrease and increase early perseverative-like behaviour, respectively. Systemic 5-HT_{2C}R antagonism additionally impairs late learning without affecting discrimination learning. These findings may have translational relevance to neuropsychiatric disorders associated with reversal learning impairments.