Serotonin 2C receptors regulate discrimination learning and cognitive flexibility by altering sensitivity to positive and negative feedback

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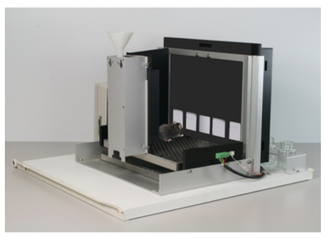
Introduction

- Multiple neuropsychiatric conditions are characterised by changes in reinforcement sensitivity. These alterations result in impairments in learning and cognitive flexibility which contribute to psychopathology and negative functional outcomes. In particular, major depressive disorder (MDD) is characterised by exaggerated sensitivity to negative feedback.
- Despite the damaging nature of such abnormalities, there is a shortage of treatment options which specifically remediate altered feedback sensitivity and the mechanisms that govern reinforcement related symptoms and behaviours are not fully established.
- We have adapted existing visual discrimination and reversal procedures for the touchscreen apparatus so that a 50% reinforced stimulus is presented in conjunction with deterministically reinforced stimuli. This innovation allows for the assessment of the influence of positive and negative associations on learning. In addition, we have implemented a within-session spatial probabilistic reversal learning (PRL) procedure in the mouse touchscreen apparatus.
- We demonstrate that performance on these tasks is dependent on serotonin 2C (5-HT2C) and 2A (5-HT2A) receptor subtypes via systemic administration of SB 242084, WAY 163909 and M100907.
- These results may have implications for the treatment of MDD and demonstrate a set of tools for the assessment of reinforcement sensitivity using the rodent touchscreen apparatus.

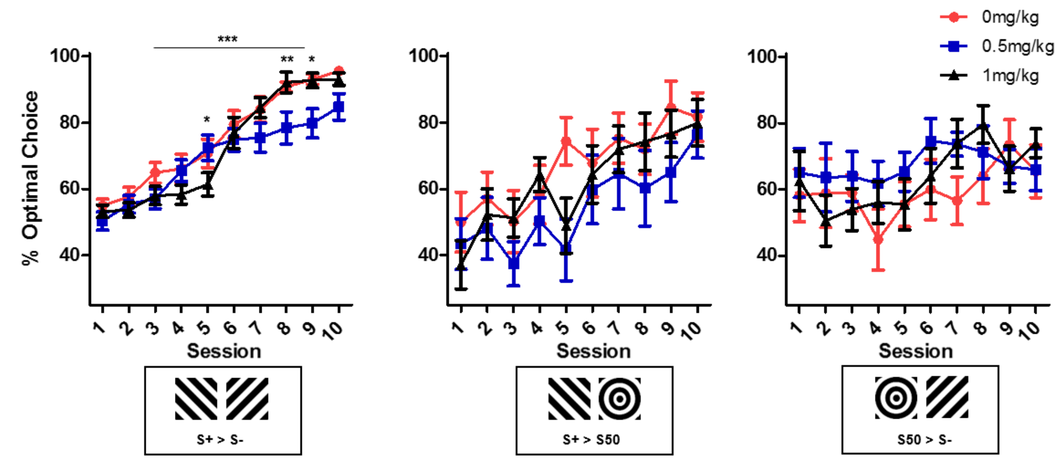
Methods

Apparatus: All experiments using mice were carried out in Bussey-Saksida touchscreen chambers (Campden Instruments Ltd., Loughborough, All behavioural schedules were controlled by ABET II Touch software. All data was committed to a database within this software. All experiments using rats were carried out in touchscreen equipped operant chambers (Med Associates Inc, Georgia, VT, USA).

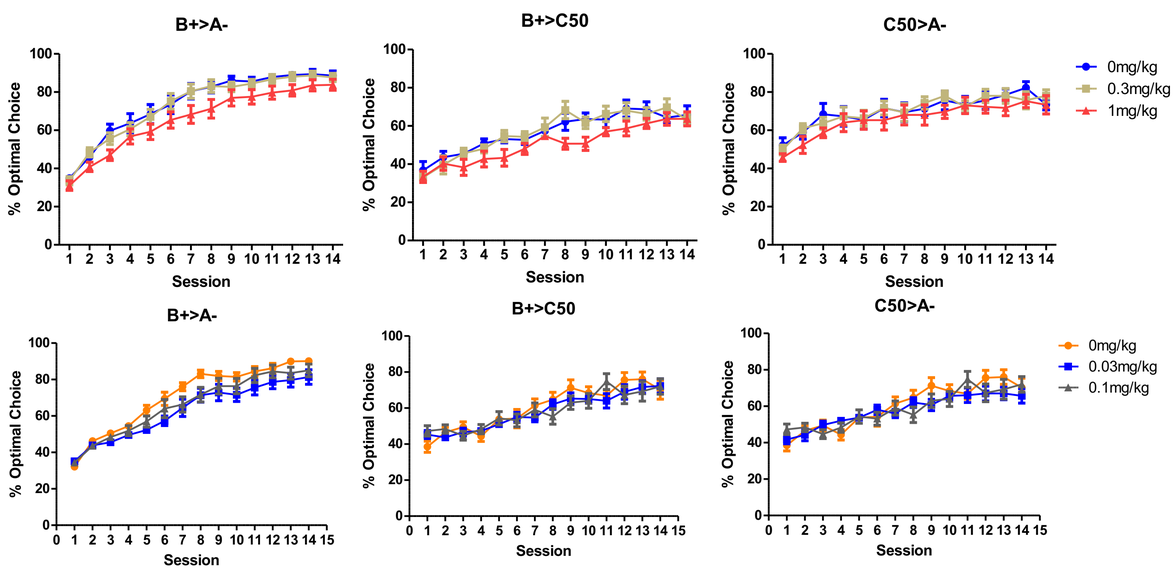


Data analysis and statistics: All measures were assessed for significance using linear mixed-modelling using the 'lme4' package in the R statistical programming language. For PRL, win-stay and lose-shift proportions were calculated by assessing the choice of mice on the trials following either a reinforced on non-reinforced trial and are taken as measures of sensitivity to positive and negative feedback respectively.

A novel valence-probe visual discrimination (VPVD) and reversal task reveals effects of 5-HT2C and 2A receptor selective compounds on learning and cognitive flexibility

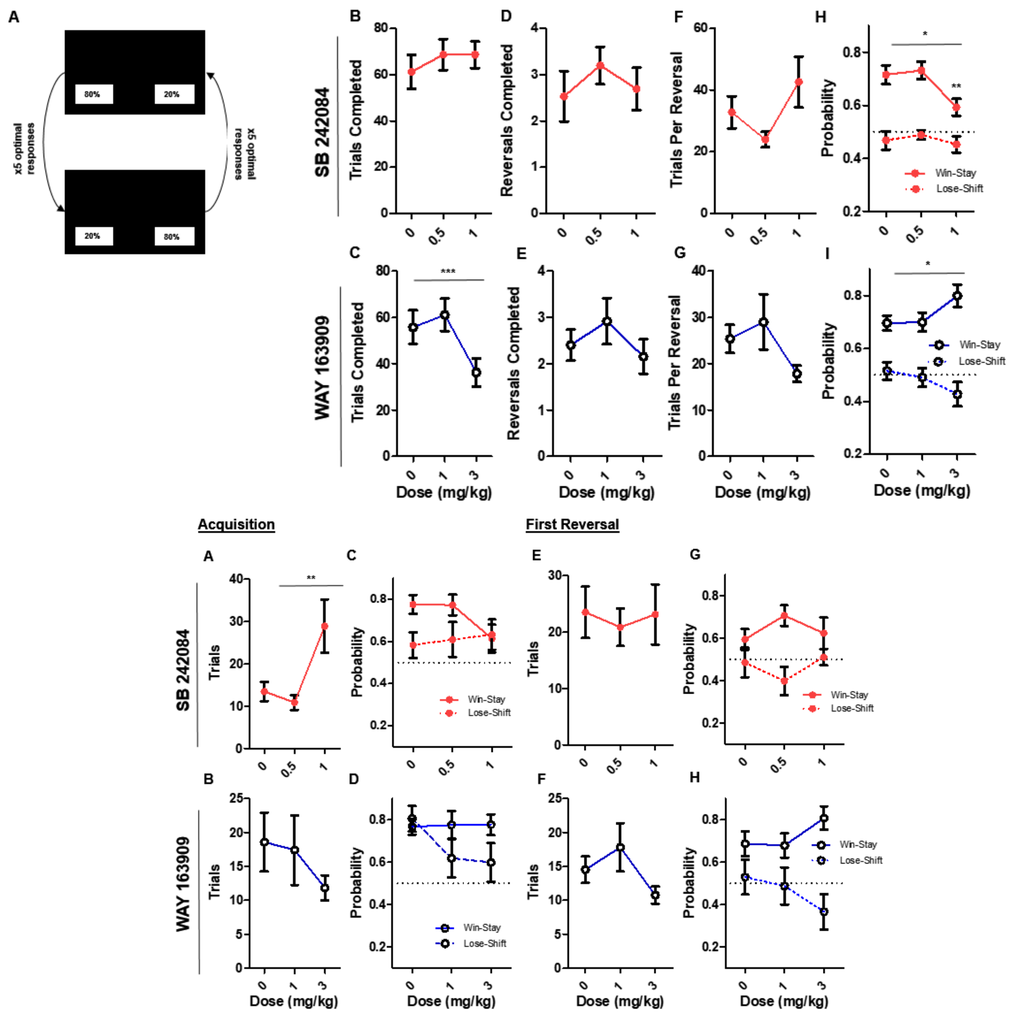


- VDVD requires animals to respond at the always-reinforced S+ and avoid the never-reinforced S-. In addition, the S+ should be selected over the 50% reinforced S50 and the S50 should be selected over the S-.
- The 5-HT2C antagonist SB 242084 was administered to male C57BL/6 mice on the VDVD task prior to behavioural sessions.
- This resulted in a task-phase, dose-dependent impairment in learning. Specifically, SB 242084 at 1mg/kg resulted in an early impairment in learning on S+>S- whilst 0.5mg/kg resulted in a late learning deficit. These changes appeared to be mediated by reduced sensitivity to positive feedback and heightened sensitivity to negative feedback.

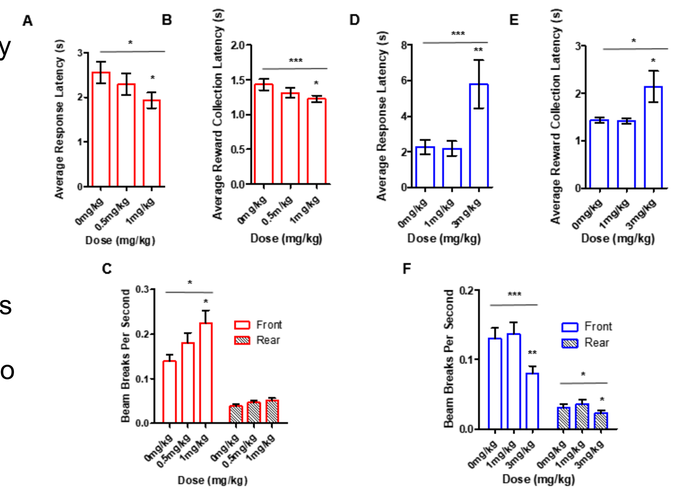


- On VPVD reversal, rats were treated with SB 242084 at 0.3mg/kg and 1mg/kg and M100907 at 0.03mg/kg and 0.1mg/kg.
- Administration of both compounds resulted in a trend toward impairment on the B+>A- trials.
- Administration of SB 242084 resulted in a significant reduction in B+>C50 trial performance overall, with the 1mg/kg dose significantly impairing performance on this trial type.

Administration of 2C selective compounds affect sensitivity to positive and negative feedback with consequent effects on cognitive flexibility



- Spatial PRL requires mice to choose between an optimal location which is 80% reinforced and a non-optimal location which is 20% reinforced. When 5 consecutive optimal responses have been emitted, the contingencies reverse and the animal must disengage from responding at the previously optimal location.
- Consistently, SB242084, the 5-HT2C antagonist at 1mg/kg, diminished sensitivity to positive feedback whilst WAY 163909 administration appeared to heighten sensitivity to positive feedback and reduce sensitivity to negative feedback.
- Administration of these compounds also resulted in changes in both reinforcer collection and choice latencies, partially consistent with non-specific changes in locomotor activity.
- These results suggest that 5-HT2CRs play an important role in the bidirectional mediation of sensitivity to reinforcement and omission of reinforcement.



Conclusions

- Changes in feedback sensitivity are recognised features characteristic of neuropsychiatric and neurodegenerative disorders, including MDD.
- Our results demonstrate that 5-HT2C receptors are a significant determinant of feedback reactivity and consequently affect discrimination learning and cognitive flexibility in the VPVD and PRL tasks.
- Across the tasks, 5-HT2C antagonism via systemic administration of SB 242084 consistently resulted in reduced sensitivity to positive feedback.
- Consequently, this compound impaired PRL performance by disrupting acquisition performance in the first phase of the task.
- 5-HT2A antagonism appeared to disrupt reversal performance.
- WAY 163909 heightened sensitivity to positive feedback and reduced sensitivity to negative feedback on PRL. This suggests that the 5-HT2C receptor might be an important target for antidepressant treatment.
- These results show that the touchscreen apparatus can readily assess reinforcement sensitivity and its effects on learning and cognitive flexibility and also provides a framework for the translational assessment of these areas in both mice and rats.
- This allows for translational assessment of rodent models of neuropsychiatric illness within a reinforcement learning framework.

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