The role of D1 and D2 pre-frontal to accumbens circuits in cognitive flexibility

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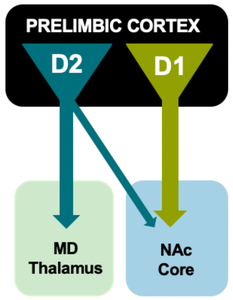
INTRODUCTION

- Flexible behavior--the ability to adapt behavior in response to changing environmental contingencies--is a critical component to everyday life.
- **Deficits in cognitive flexibility is one of the most consistently documented cognitive problems in psychiatric and neurodevelopmental disorders including major depression, schizophrenia, autism, obsessive compulsive disorder, and addiction.**
- In order to adaptively respond to changes in the environment, one must suppress irrelevant and unsuccessful strategies, come up with new ones and maintain them if they prove to be effective.
- This behavior relies on coordinated activity of distinct neurons in the **prelimbic region (PrLC)** of the prefrontal cortex – a brain region that projects to regions such as the **mediodorsal thalamus (MDT)** and **nucleus accumbens core (NAc)** and is critically involved in decision-making. [1-4]

Figure 1: Working Model of Circuits Mediating Cognitive Flexibility

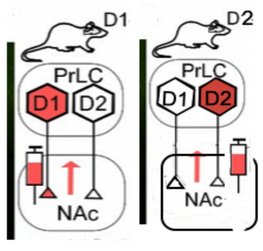


- Recent findings by the Hearing lab have shown that deficits in cognitive flexibility produced by prolonged exposure to psychosocial stress aligns with distinct (opposing) changes in the function of two different types of pyramidal neurons in the PrL-PFC - those expressing **dopamine type I receptors** or **dopamine type II receptors**[5]. Although not exclusive, PrLc-MDT circuits express D2 receptors and PrLC-NAc circuits express both D1 and D2, with greater number of neurons expressing the type I receptors [6-8] (Figure 1). Accordingly, **this project tested the hypothesis that PrL-PFC D1 and D2 pyramidal neurons that project to the nucleus accumbens core (NAc) play distinct roles in facilitating cognitive flexibility.**

METHODS

Transgenic Animals: To selectively target D1- versus D2-NAc pyramidal neurons, transgenic (D1- or D2-cre) mice that express the enzyme, Cre-recombinase, in D1- or D2-receptor expressing neurons were used.

Surgery and Chemogenetic Manipulation: A retrograde virus (rAAV-hsyn-d10-hm4Di-(Gi)-mcherry) that promotes the expression of an inhibitory G-protein coupled receptor called *DREADDs* (Designer Receptor Exclusively Activated by Designer Drugs) was infused in the *Nucleus Accumbens Core (NAc)* of D1- or D2-cre mice.



Due to retrograde movement of the virus, it was expressed in the *PrLC*, where a guide cannula was implanted to deliver *CNO (clozapine-n-oxide)* on the day of the ED shift (see below). CNO activates the inhibitory G-protein coupled receptor, in effect, inhibiting either D1 or D2 pyramidal neurons in the PrLC that project to the nucleus accumbens core (NAc).

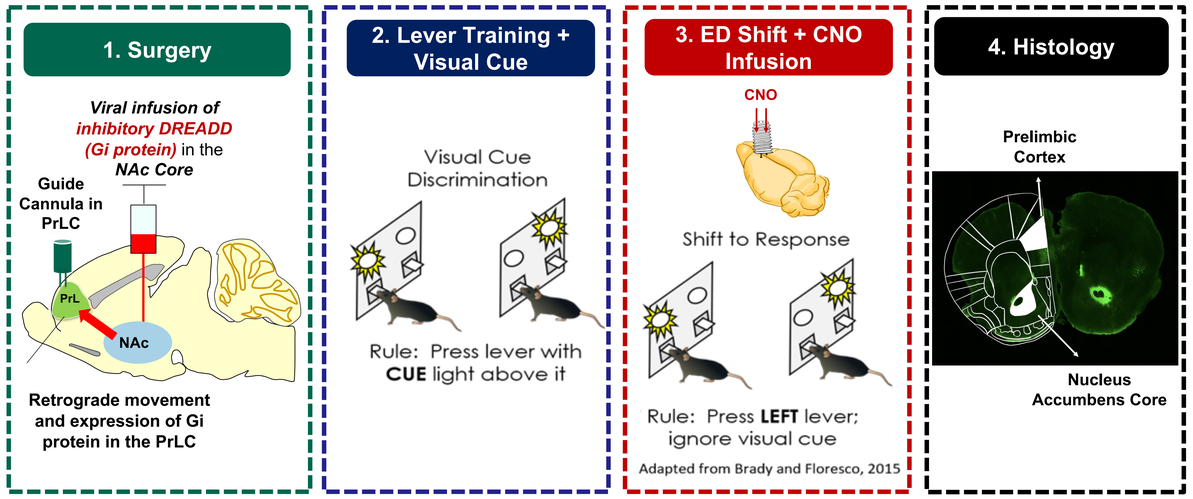
Behavior: Attention Set Shifting Task

Food Training: Mice were food deprived for the entirety of this task. Mice were habituated in operant conditioning boxes to press a lever to receive an Ensure reward.

Lever Training: Following food training, animals underwent lever training until they omitted less than five total trials for two consecutive days, after which a lever preference was assessed with a bias test.

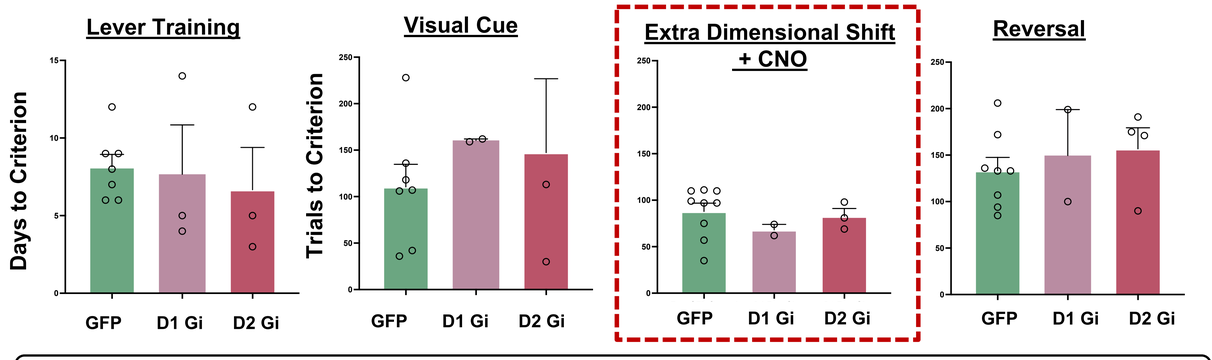
Testing: The animals underwent **visual cue testing, extra dimensional (ED) set shift test, and reversal test.** Mice received CNO (clozapine-n-oxide) on the day of the ED shift. **A streak of ten consecutive correct responses** determined the criterion for passing on to the next test the following day. The active lever for the set shift task was the opposite of the mouse's bias, while reversal task used the mouse's preferred lever.

EXPERIMENTAL TIMELINE

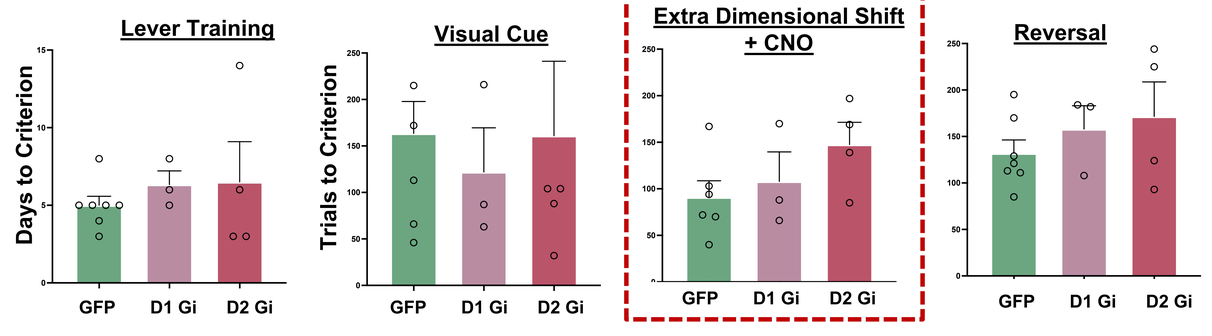


RESULTS

Inhibition of D1 and D2 expressing PrLC-NAc neurons *does not affect* cognitive flexibility in females



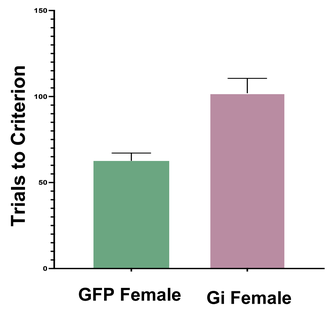
Inhibition of D2 expressing PrLC-NAc neurons *impairs* cognitive flexibility in males



CONCLUSIONS

- Current data suggests that D2 receptor expressing pyramidal neurons in the prelimbic cortex that project to the nucleus accumbens core preferentially facilitate flexible decision making in males.
- Our past findings have demonstrated that inhibition of the prelimbic cortex in females impairs performance on the extra-dimensional shift of the Attention Set Shifting Task (see figure below).
- The lack of effect on cognitive flexibility after inhibition of the D2 PrLC-NAc sub-circuit in females may suggest a preferential involvement of PrLC-NAc neurons that express D1 receptors in regulating cognitive flexibility.

Inhibition of PrLC impairs cognitive flexibility in females



- Additionally, it is plausible that alternative projections from the prelimbic cortex e.g., the PrLC-MDT circuit that primarily expresses dopamine type II receptors might be more important for mediating cognitive flexibility in females.

FUTURE DIRECTIONS

- Increase the sample size to increase the power of statistical analysis
- Manipulate the PrL-MDT circuit and investigate its distinct role in facilitating cognitive flexibility

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