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Striatal and Reward-Related Function in a Mouse Model for Fragile X Syndrome

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Introduction

Fragile X syndrome (FXS) is the leading genetic cause of autism. FXS is a syndromic form of autism caused by a mutation of the *Fmr1* gene located on the X chromosome that produces the fragile X mental retardation protein (FMRP). FMRP is essential for healthy brain development. According to the CDC, 4 out of 10 individuals diagnosed with autism were also diagnosed with fragile X syndrome. Patients with fragile X syndrome often display reward deficits due to the absence of FMRP, which is needed for reward learning. In this study, we observed the dorsal striatum (DS) and nucleus accumbens (NAc) of mice models due to their function in regulating reward behavior, memory, learning, motor function, and reinforcement. Using *Fmr1* knockout (KO) and wild type (WT) mice models for FXS, we observed cocaine-related reward deficits in the *Fmr1* KO mice using an operant cocaine intravenous self-administration assay (IVSA). However, when using food as a reinforcer, we did not observe any natural reward deficits in the KO mice. In addition, we wanted to explore the effects of FMRP in cholinergic cells (figures 2 and 3) and its role in social interactions to better understand FXS and related behaviors through social conditioned place preference (sCPP) on WT, KO, and mice models for fragile X syndrome lacking the *Fmr1* gene in cholinergic cells (cKO).

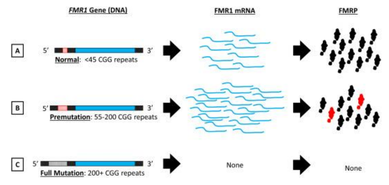


Figure 1: Mutation of the *Fmr1* Gene

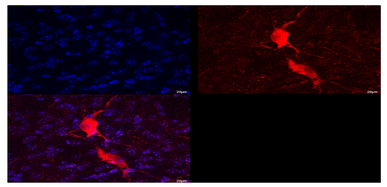


Figure 2: ChAT (red) and DAPI (blue). Scale bars = 20 µm.

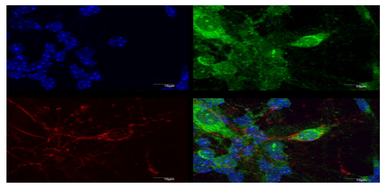


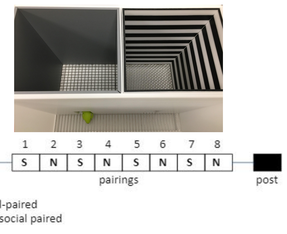
Figure 3: Co-localization of FMRP (green), ChAT (red), and DAPI (blue). Scale bars = 10 µm.

Methods

Operant Conditioning: Using food operant conditioning and intravenous self administration in two separate studies, we were able to study drugs of abuse and food as reinforcers for reward learning in *Fmr1* KO and WT mice. An operant conditioning chamber containing active and inactive nosepoke ports for the mice to self administer either intravenous cocaine, or food via a liquid dipper containing Ensure®, allowed us to observe acquisition of the reinforcers consumed followed by the extinction of intake behavior. Dose-response testing occurred after extinction to measure the effects of reinforcer concentrations.

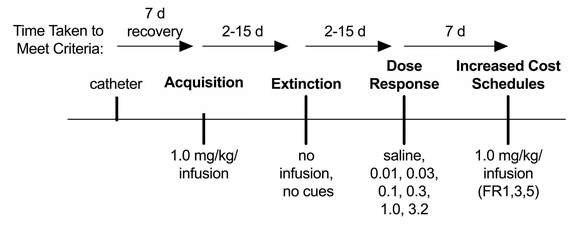
Social Conditioned Place Preference (CPP):

Conditioned place preference was utilized to analyze social preferences and deficits in *Fmr1* KO, cKO, and WT mice through a series of 3 chambers. The main chambers contained either white and black striped walls with wire-grid flooring or grey walls and larger wire-grid flooring. The neutral chamber contained white walls and a metal bar floor, which allowed the mice to travel between the main chambers during the pre and post-tests. During conditioning, a "stranger" mouse (same age, same sex) under a wire cup or an empty wire cup were presented on alternating days in opposite main chambers. At pre- and post-test, social preferences in the KO mice compared to the WT were measured in the absence of the social companion. Using video-tracking techniques via infrared cameras, we were able to measure time spent in the social-paired versus non-social-paired chambers.

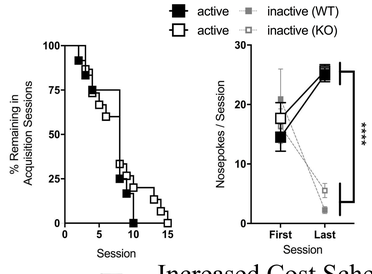


The Presence of FMRP Promotes Addiction-Like Behavior During Cocaine Self-Administration

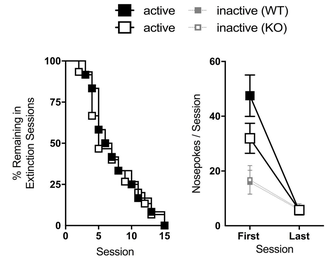
A Experimental Timeline for Mouse Cocaine IVSA



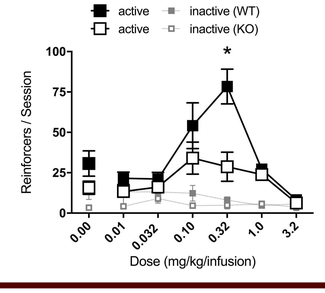
B Acquisition



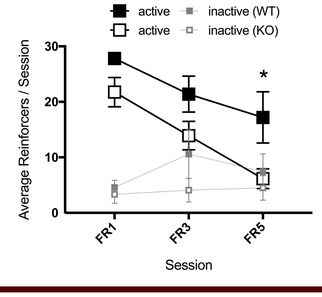
C Extinction



D Dose-Response

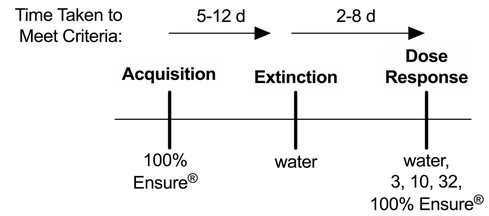


E Increased Cost Schedules

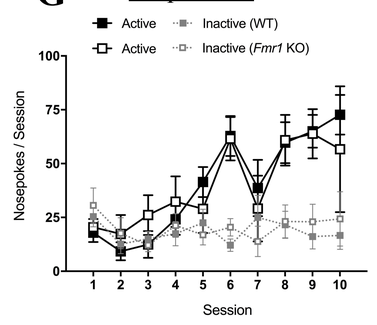


Fmr1 KO Mice Exhibit Normal Natural Reward Function and Learning Abilities Following Food Operant Conditioning

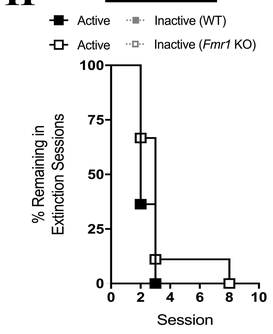
F Experimental Timeline for Mouse Food Operant Conditioning



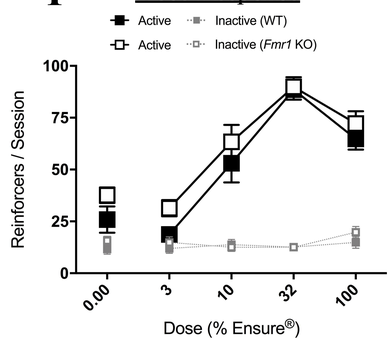
G Acquisition



H Extinction

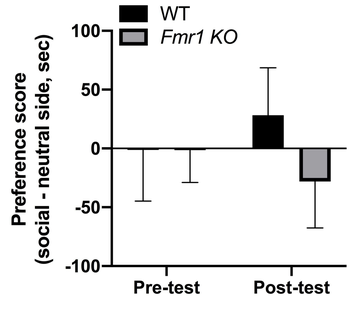


I Dose Response

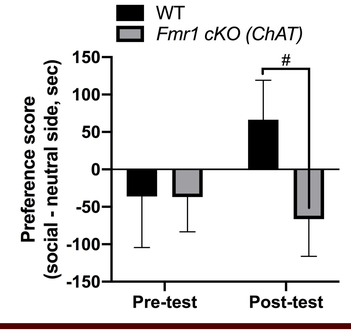


The Absence of FMRP in Cholinergic Cells Results in Social Deficits

J Social CPP w/ *Fmr1* KO mice



K Social CPP w/ *Fmr1* cKO mice



Conclusions

- The absence of FMRP results in the impairment of cocaine-induced reward learning, while using a natural food reinforcer does not result in reward deficits. This finding suggests that FMRP helps to facilitate drug addiction behaviors.
- Although there were no significant social preference differences between the WT and *Fmr1* KO mice, there was a trend towards a significant difference between social behaviors in *Fmr1* cKO and WT mice. The *Fmr1* cKO mice displayed social reward deficits, suggesting that FMRP may serve an important function in cholinergic cells with regard to social behavior.

Acknowledgements

Salcedo-Arellano, M. J., Dufour, B., McLennan, Y., Martinez-Cerdeno, V., & Hagerman, R. (2020). Fragile X syndrome and associated disorders: Clinical aspects and pathology. *Neurobiology of disease*, *136*, 104740.

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