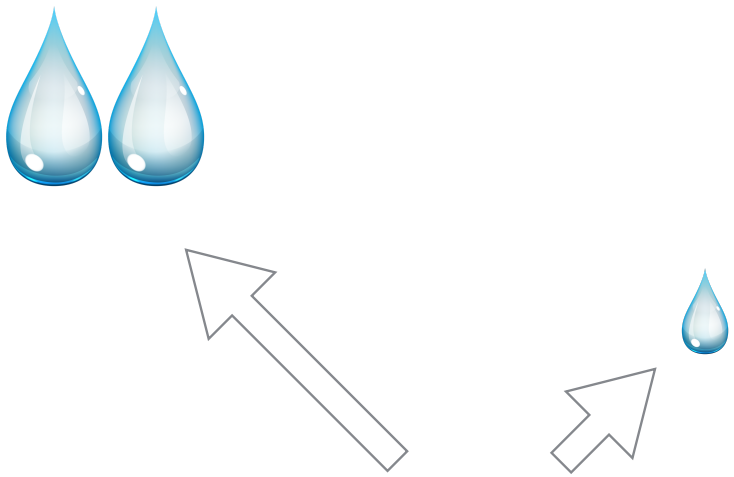
Control of Intertemporal Choice by Dorsal Raphe Serotonergic Neurons

Sangyu Xu (IMCB, Singapore)

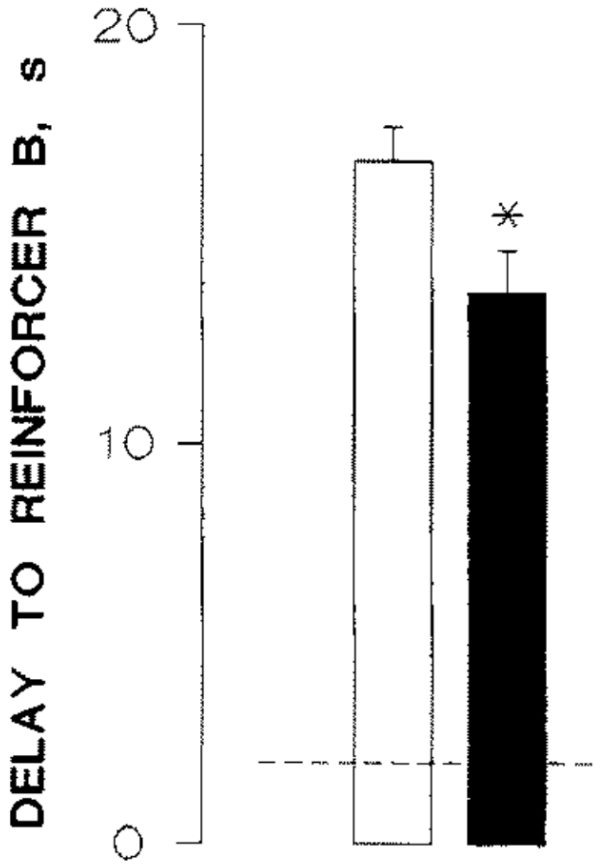
March, 2019, CoSyNe 5-HT Workshop, Cascais, Portugal

$10 today or $20 in a week?

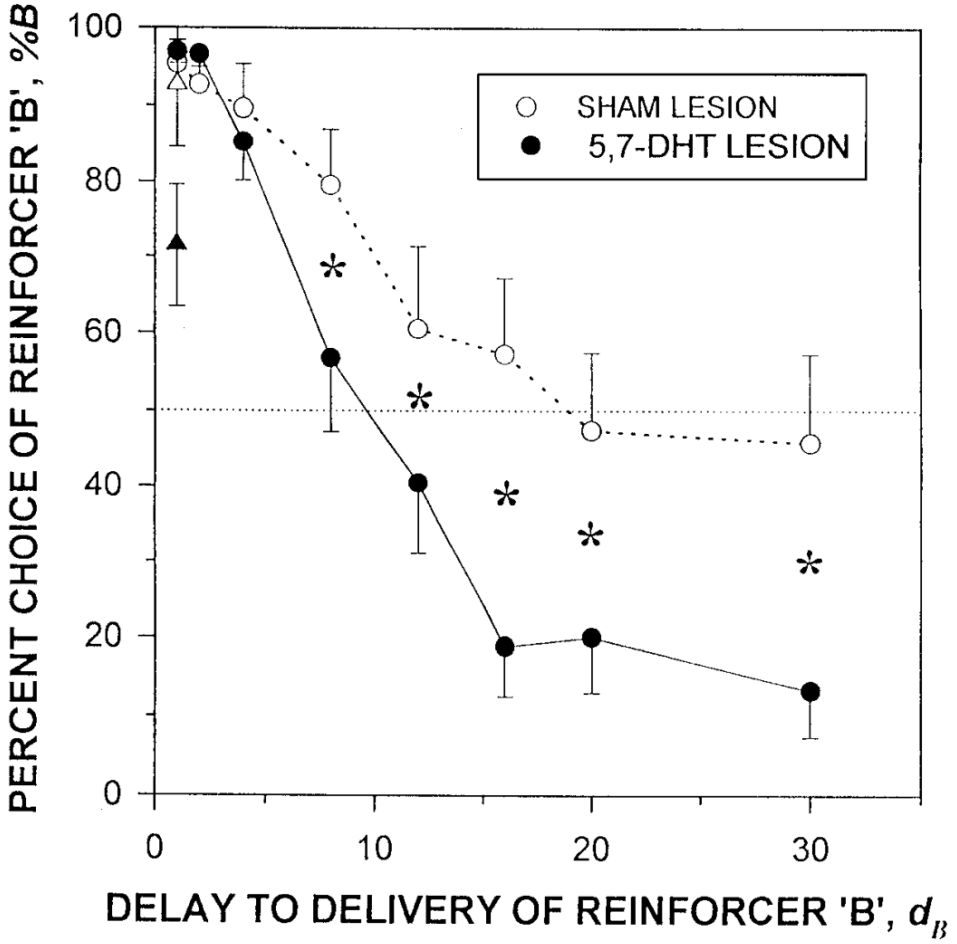
1 drop of water in 2 seconds or 2 in 10 seconds?



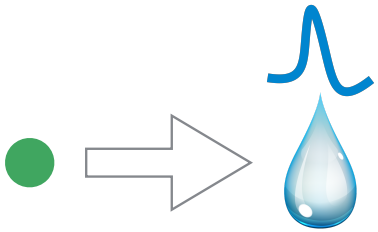
Dorsal Raphe Serotonin Lesion Causes Impulsive Choice in the Rat



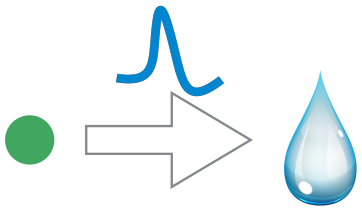
Wogar *et al.* (1993)



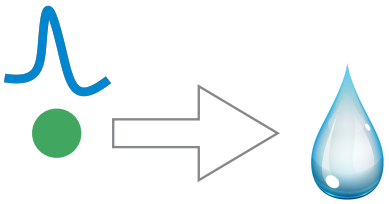
Mobini *et al.* (2000)



Unconditioned Reward (Liu *et al.*, 2014)

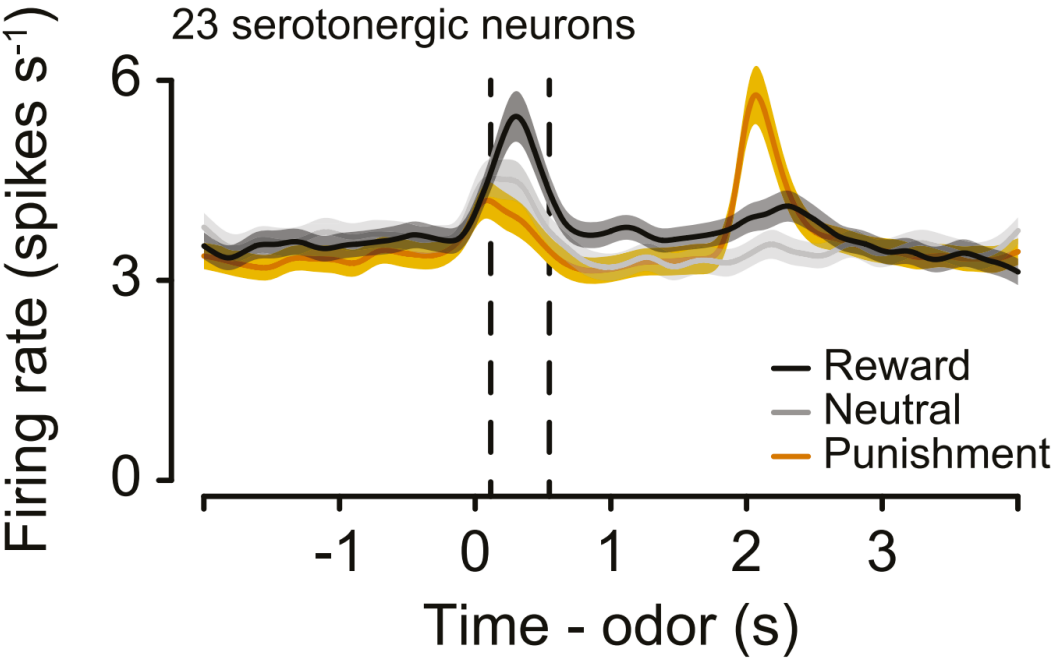


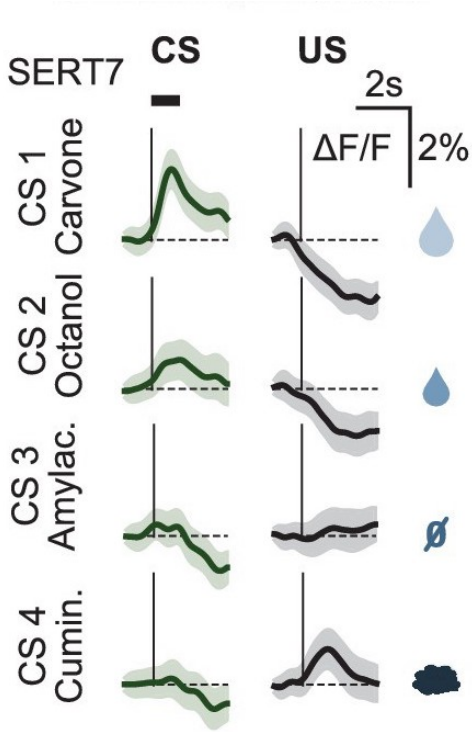
Reward anticipation (Miyazaki *et al.*, 2015, Fonseca *et al., 2015*)

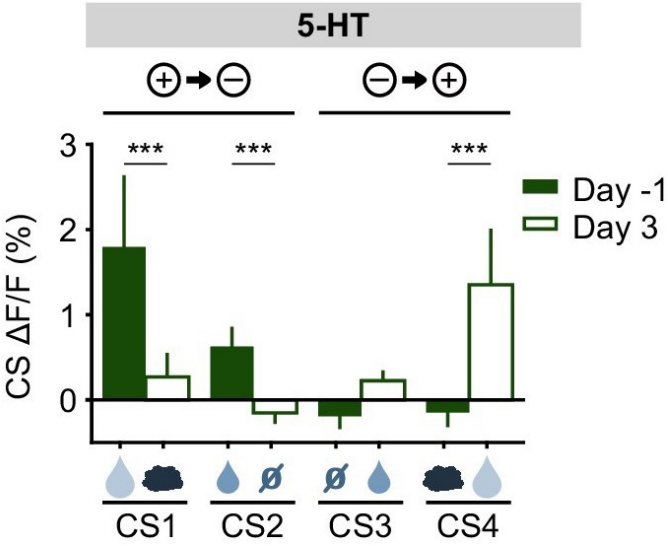


Reward prediction (Cohen *et al.*, 2014, Matias *et al., 2017*)

DR Serotoninergic Neurons Encode Reward Value at Cue



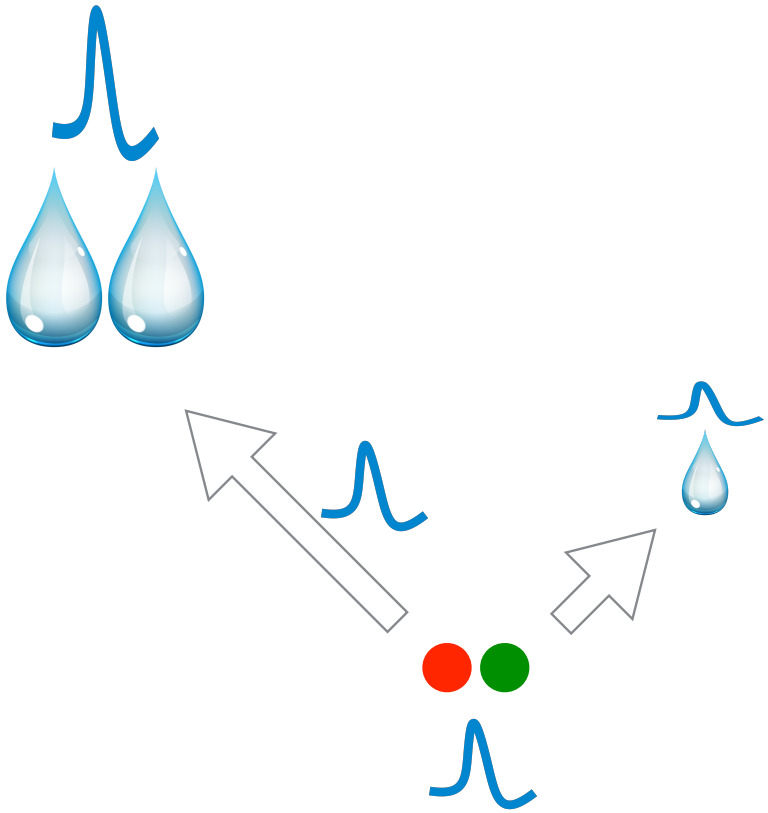




Cohen *et. al.* (2014)

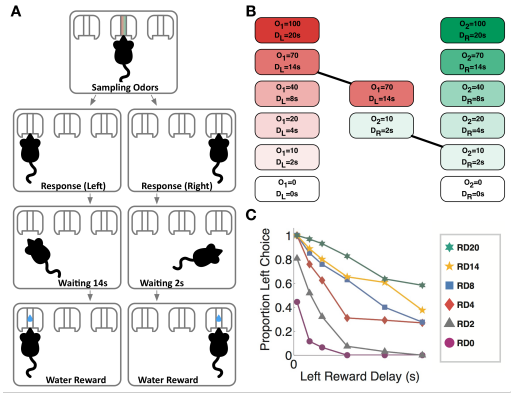
Matias *et. al.* (2017)

Serotonin in Intertemporal Choice



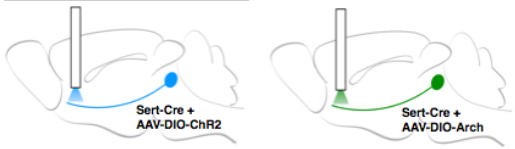
Overview

1. Odor-Guided Intertemporal Choice Task



2. Role of DR Serotonergic Neurons

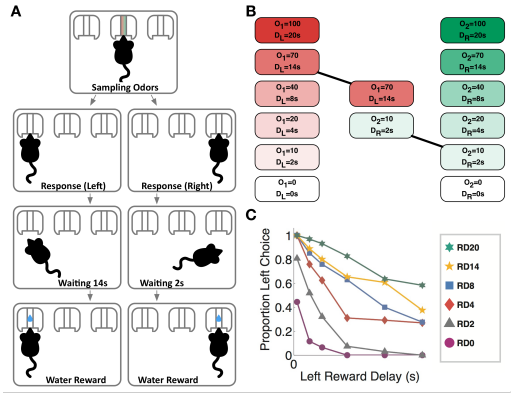
3. Circuit mechanism



Overview

1. Odor-Guided Intertemporal Choice Task

   Mice can do

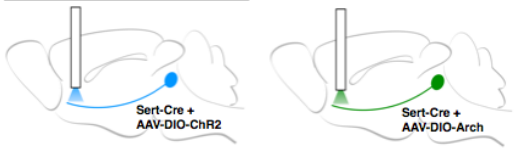


2. Role of DR Serotonergic Neurons

   DR Suppresses choice impulsivity

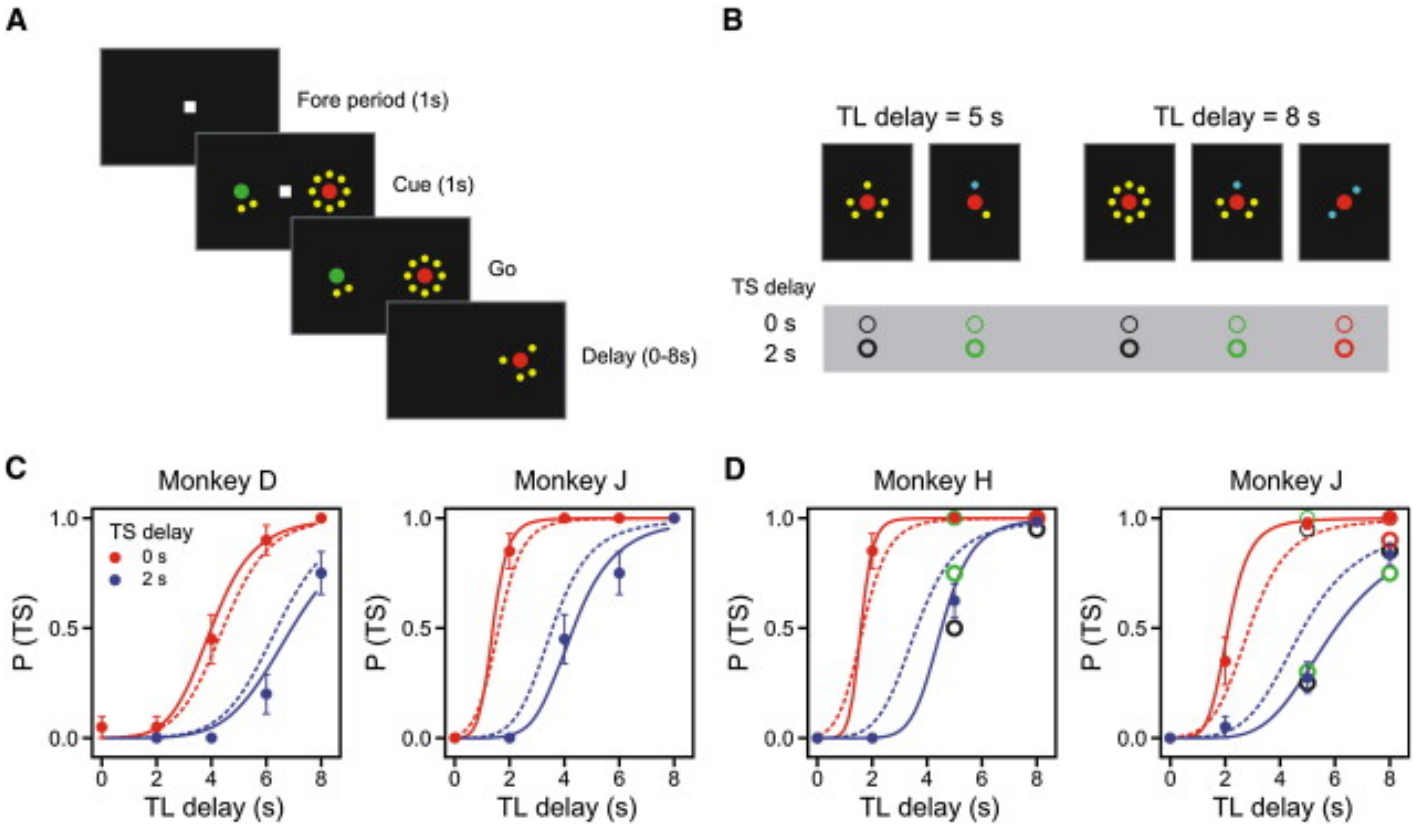
3. Role of DR Serotonergic Neurons

   NAcSh possible target

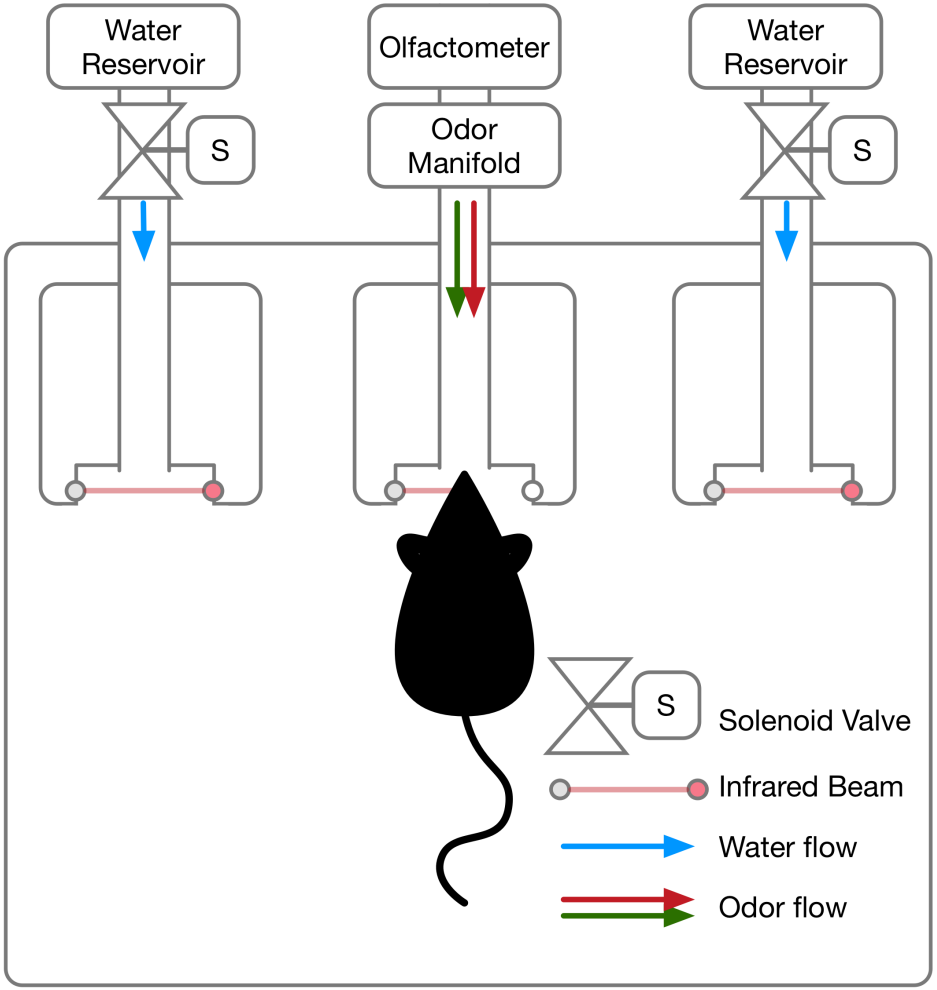


Part 1
Task: Key Design Features

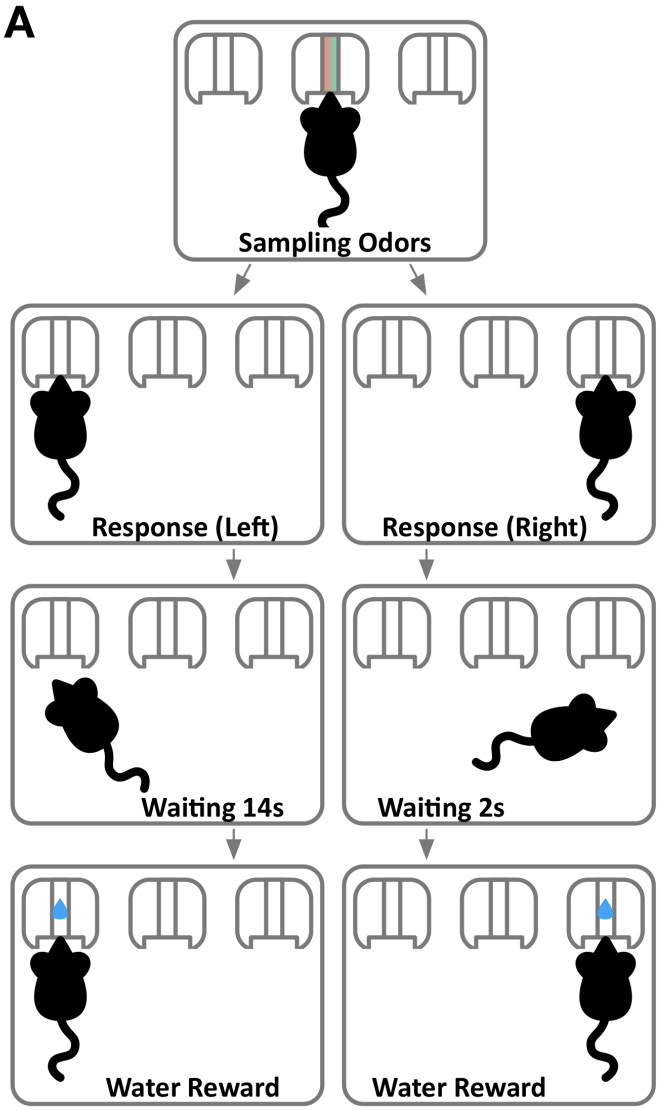
- Symmetrical choice task
- Isolated decision epoch
- Interleaved reward contingencies
- Testing waiting specifically



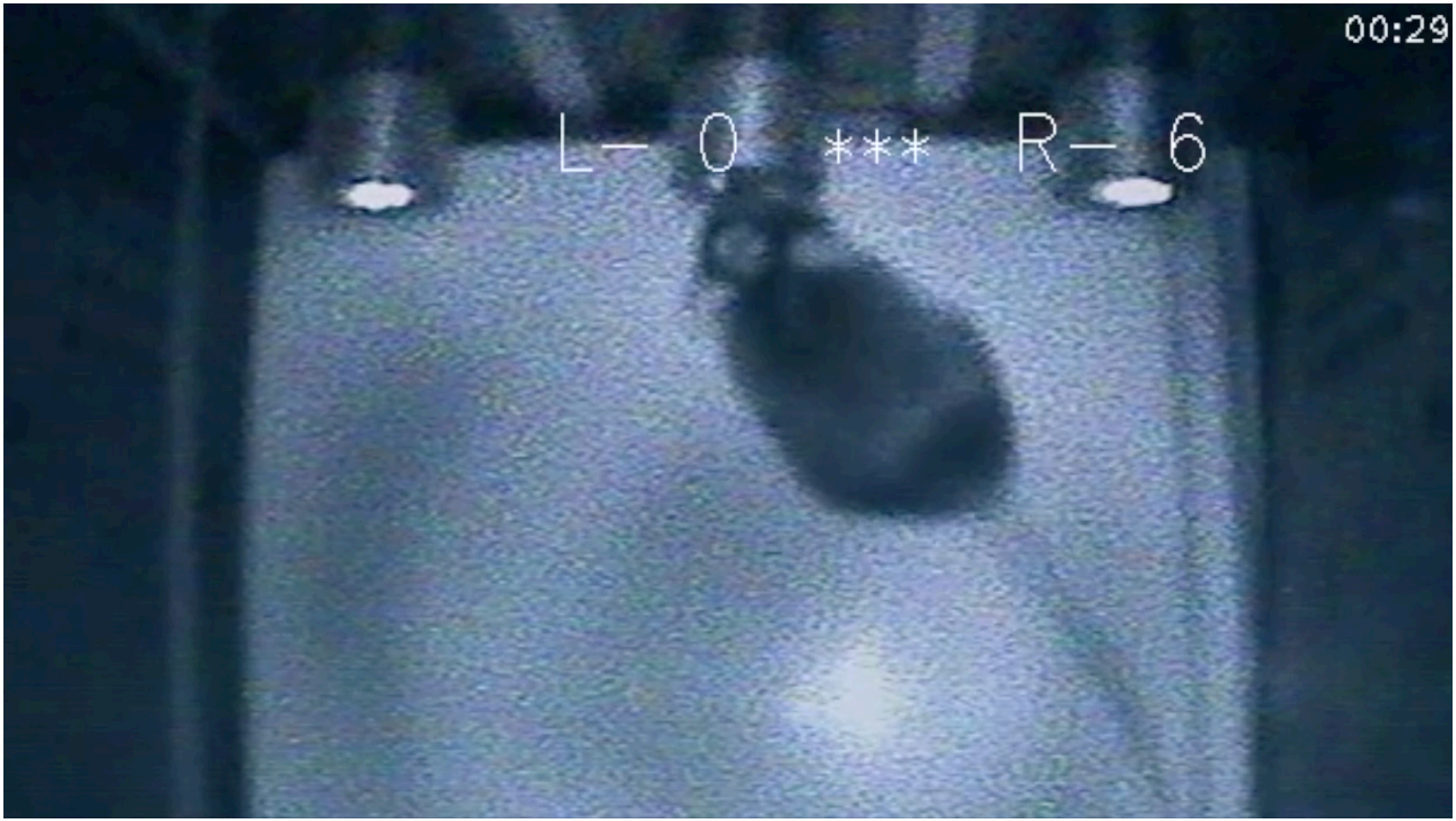
Kim *et al.* (2008)


Water Reservoir
Olfactometer
Water Reservoir
S
Odor Manifold
S
S
Solenoid Valve
Infrared Beam
Water flow
Odor flow

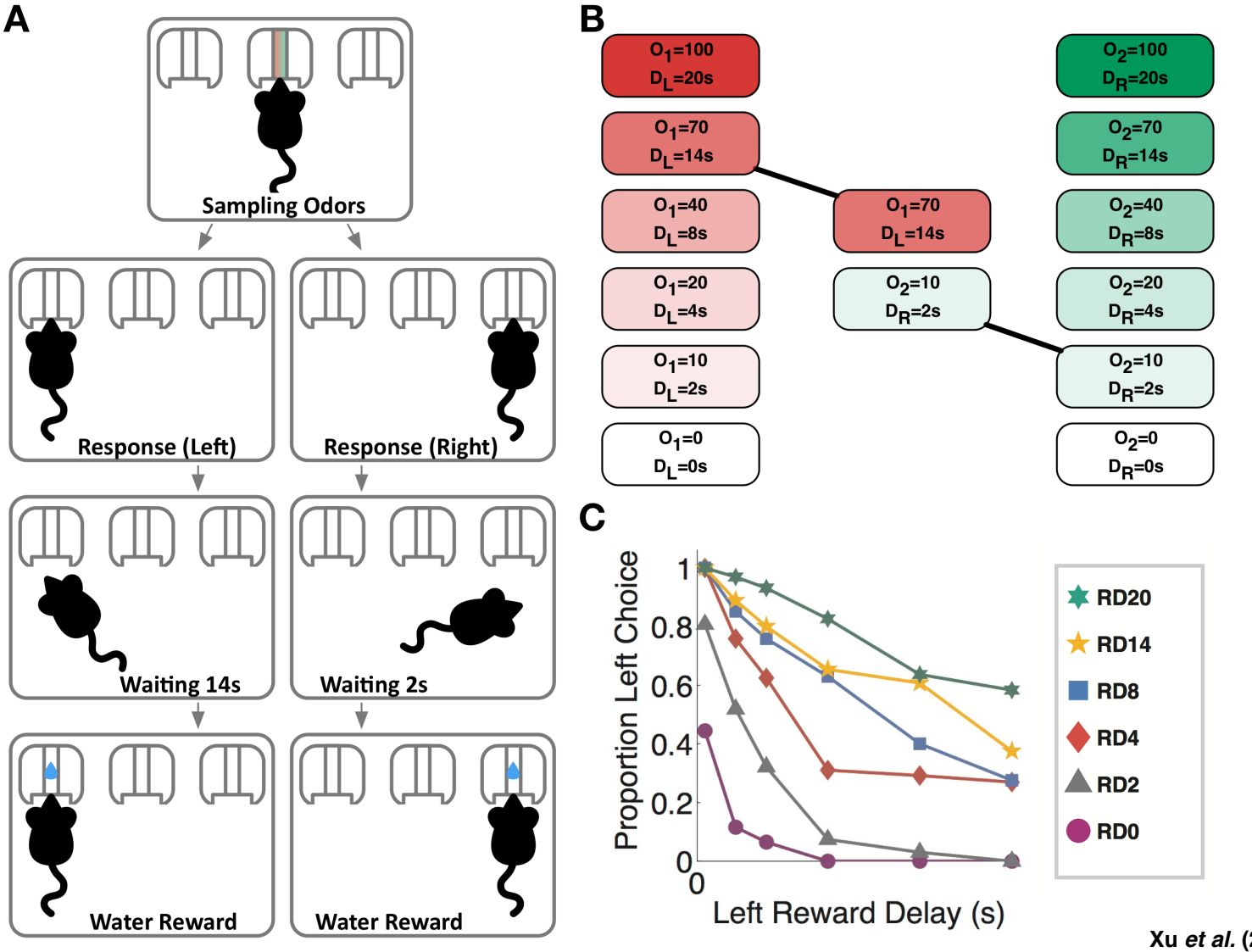
The Odor-Guided Intertemporal Choice Task



Xu *et al* (2017)

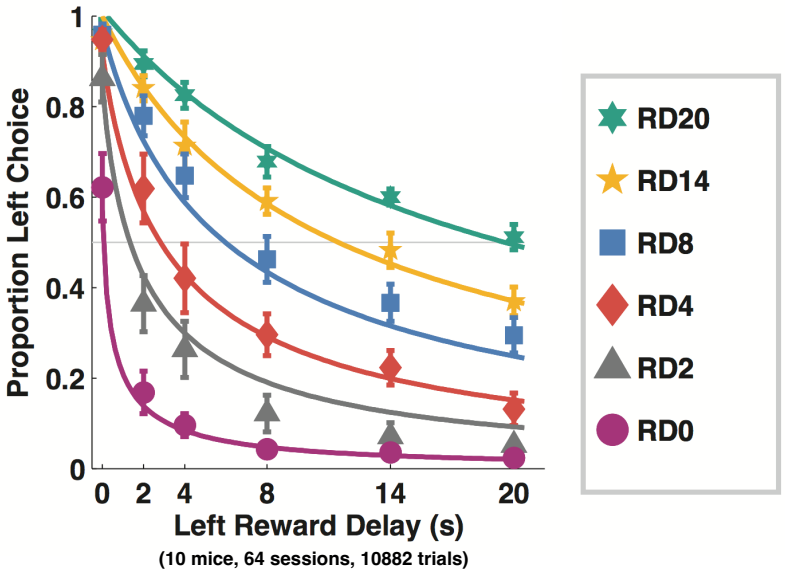

00:29
L- 0 *** R- 6

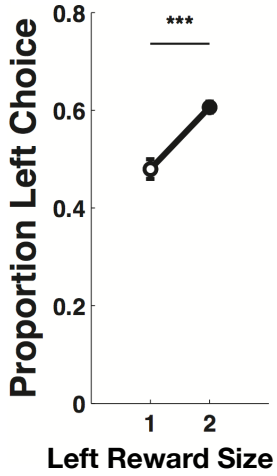
The Odor-Guided Intertemporal Choice Task



Xu *et al.* (2017)

Mice in OGIC Task are Sensitive to Reward Delay and Size





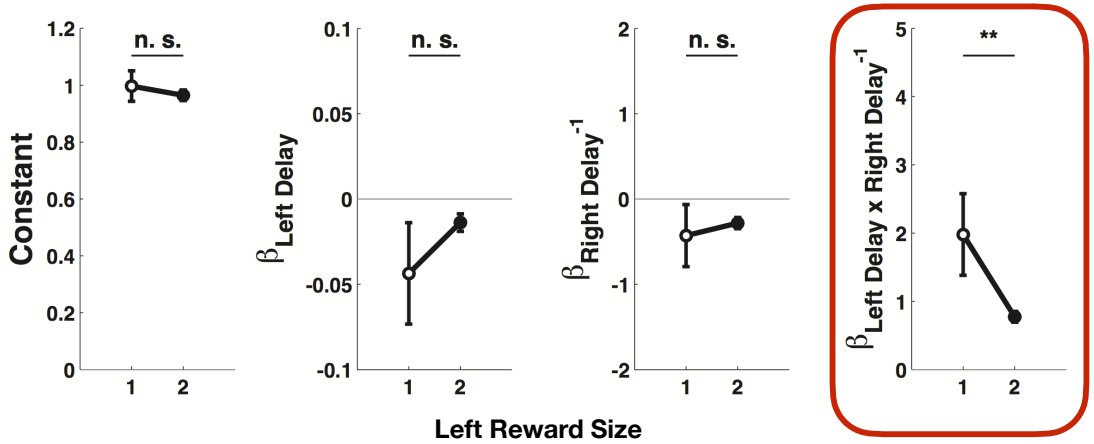
GLM Terms:

constant,

$\beta_{\text{Left Delay}}$ x Left Delay,

$\beta_{\text{Right Delay}^{-1}}$ x Right Delay^{-1}

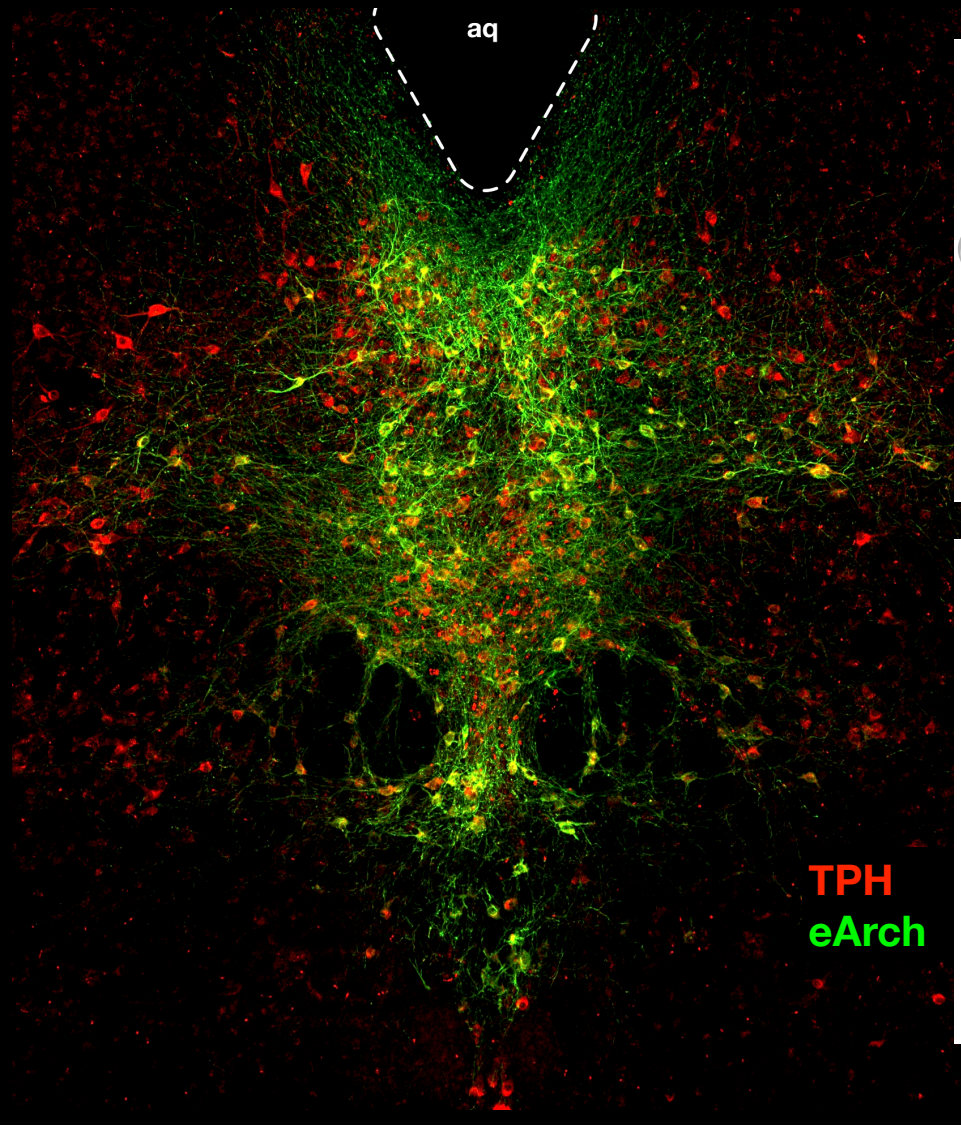
$\beta_{\text{Left Delay*Right Delay}^{-1}}$ x Left Delay x Right Delay^{-1}

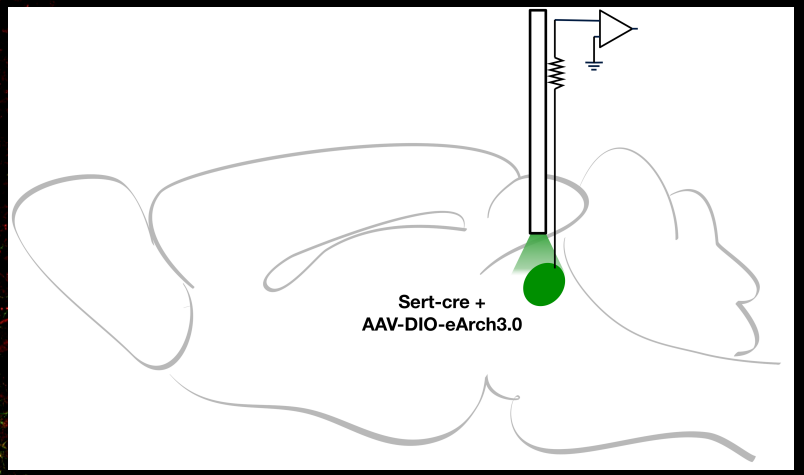


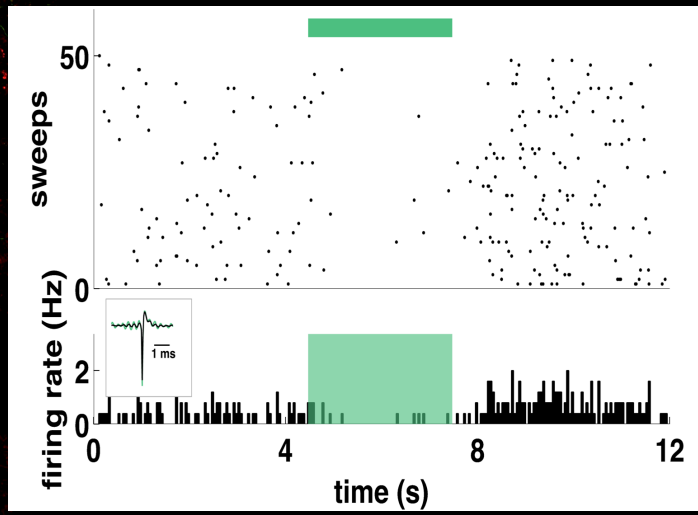
Xu *et al* (2017)

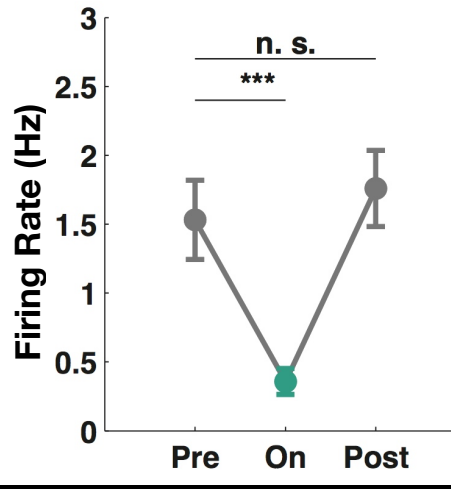
Part 2
Serotonin Involvement

Optogenetic Inhibition of Serotonergic Neurons



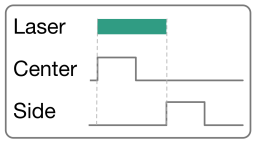




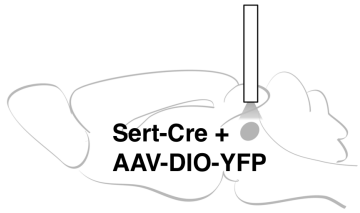


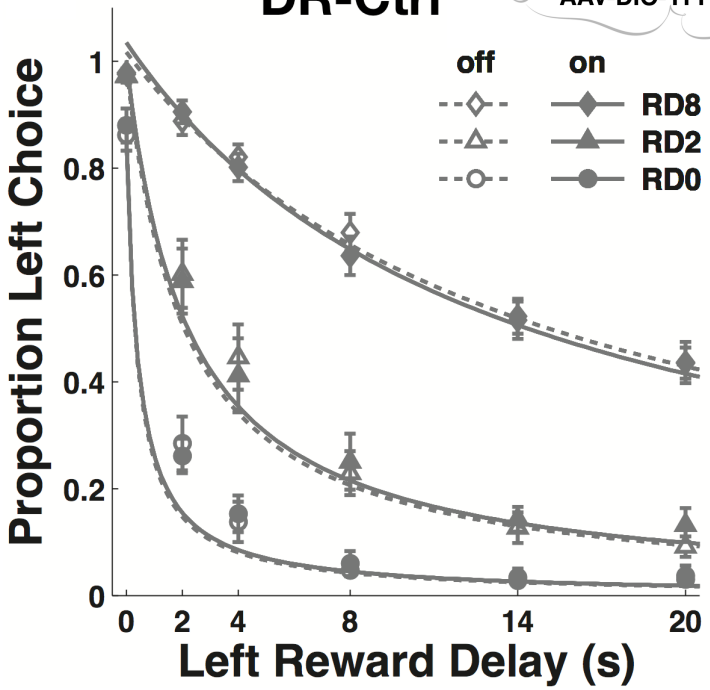
Xu *et al* (2017)

Inhibiting DR 5-HT Neurons Increased Choice Impulsivity

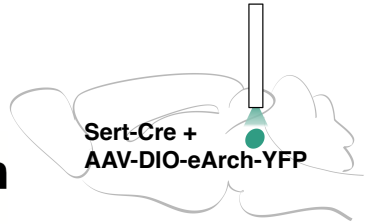


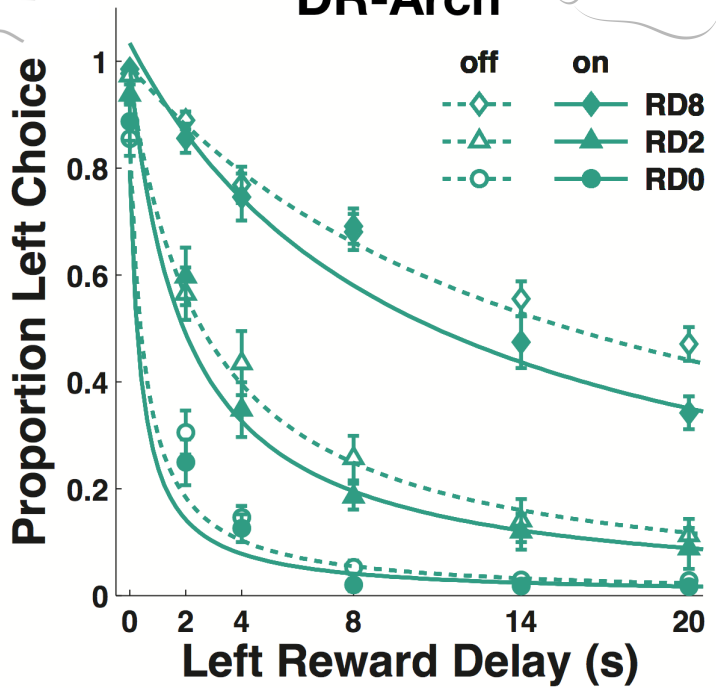
10%-20% Trials Light On
80%-90% Trials Light Off





10 mice, 20473 trials, 132 sessions

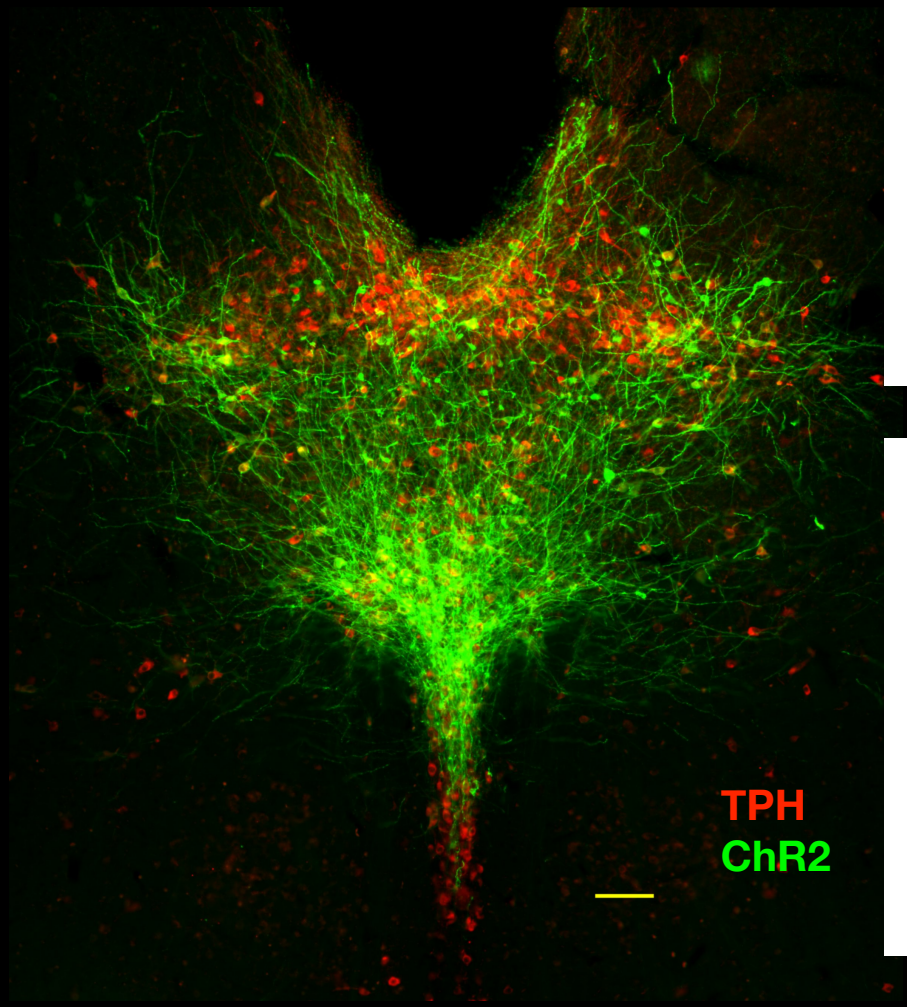


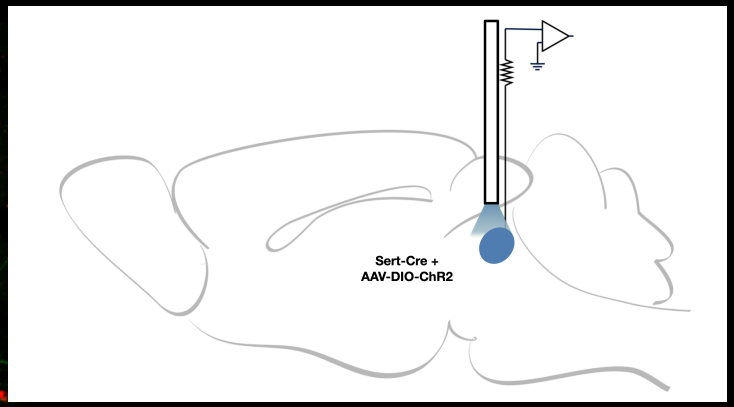


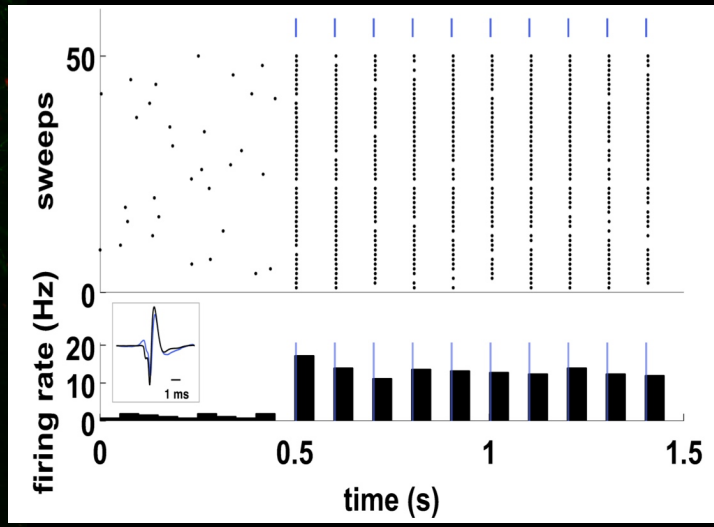
10 mice, 20785 trials, 137 sessions

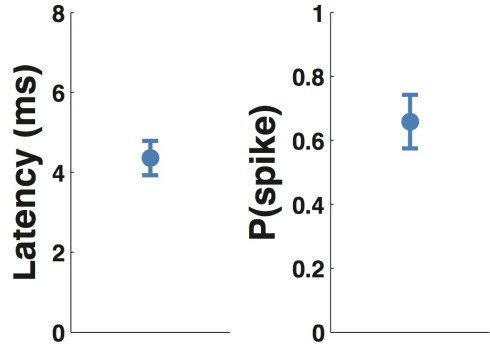
Xu *et al* (2017)

Optogenetic Excitation of Serotonergic Neurons









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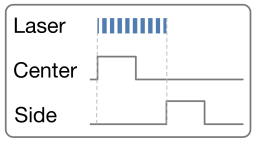
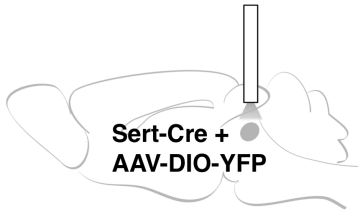
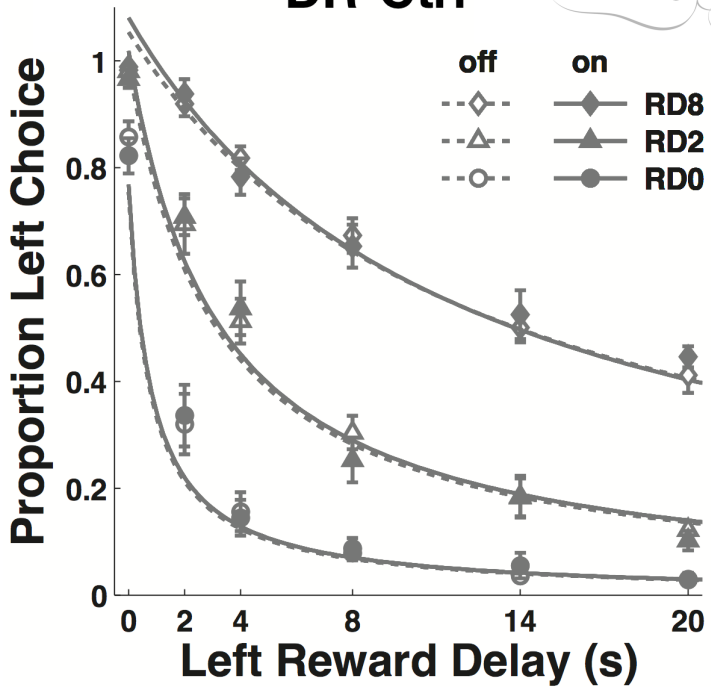
Activating DR 5-HT Neurons Reduced Choice Impulsivity



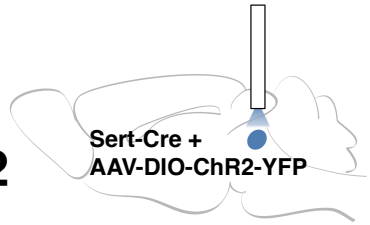
10%-20% Trials Light On
80%-90% Trials Light Off



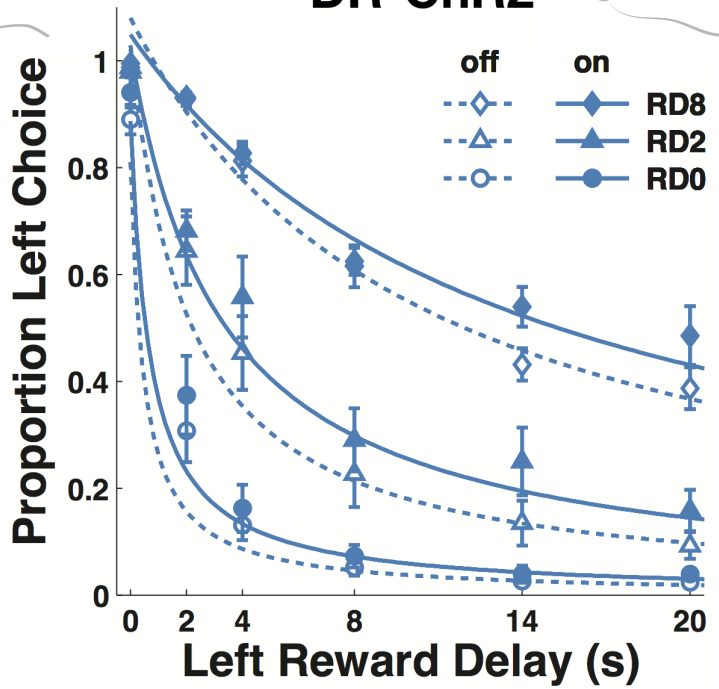
DR-Ctrl



10 mice, 20712 trials, 140 sessions



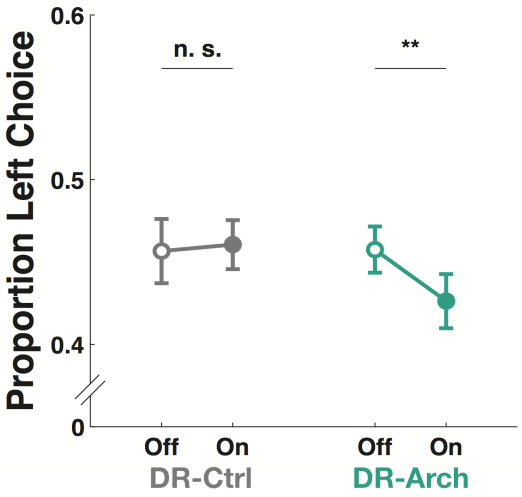
DR-ChR2

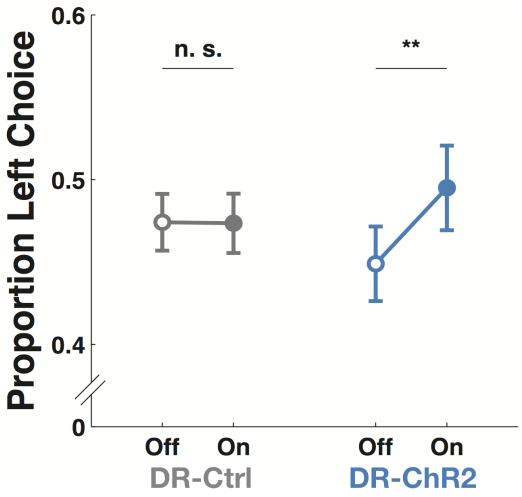


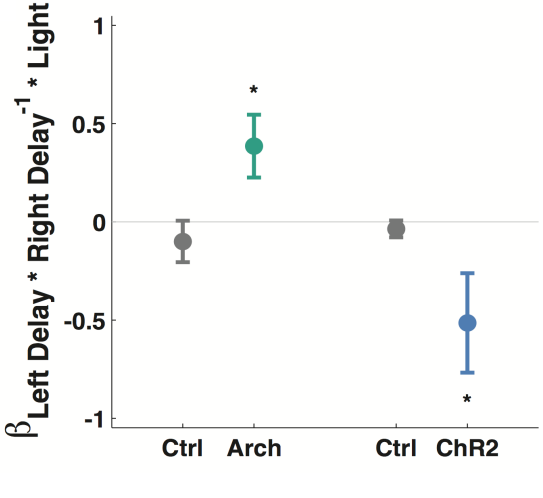
10 mice, 20455 trials, 147 sessions

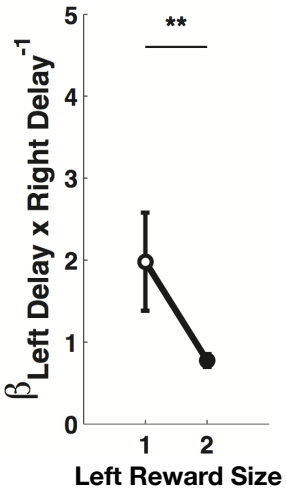
Xu *et al* (2017)

DR 5-HT Neurons Regulate Choice Impulsivity Bi-directionally



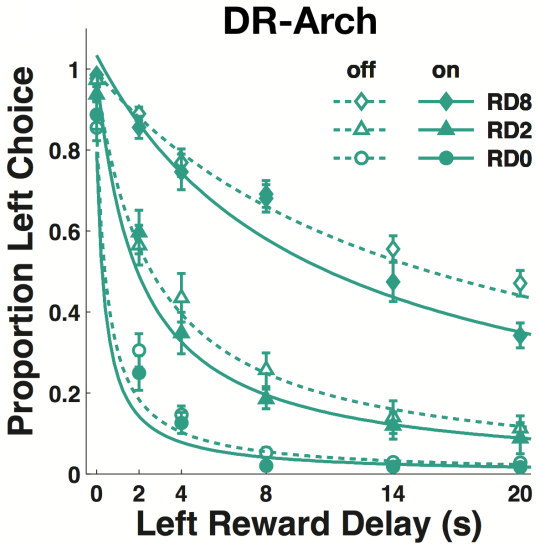


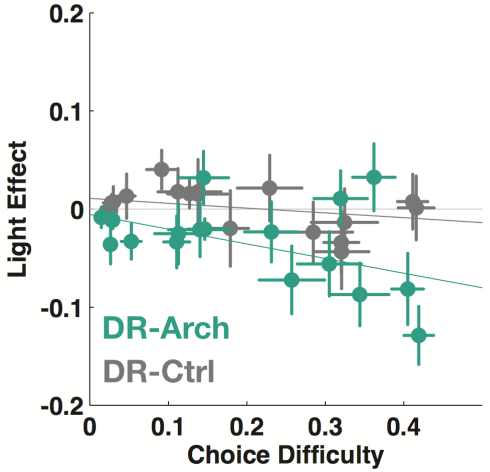


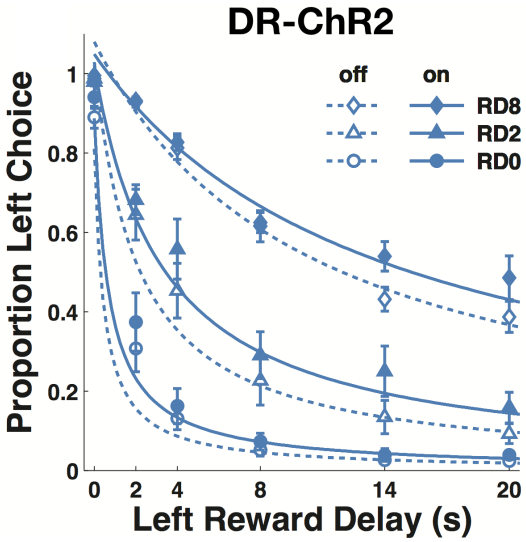


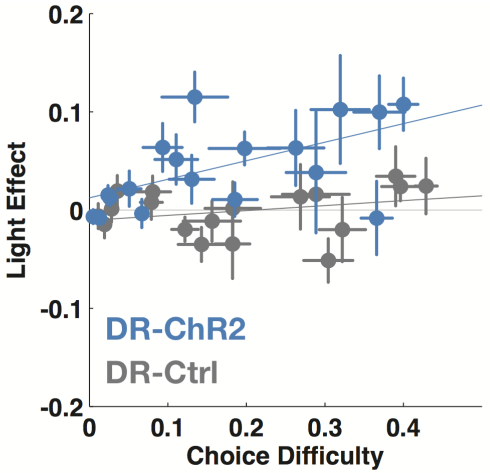
Xu *et al* (2017)

5-HT Effects are not Uniform across Sampled Delay Space



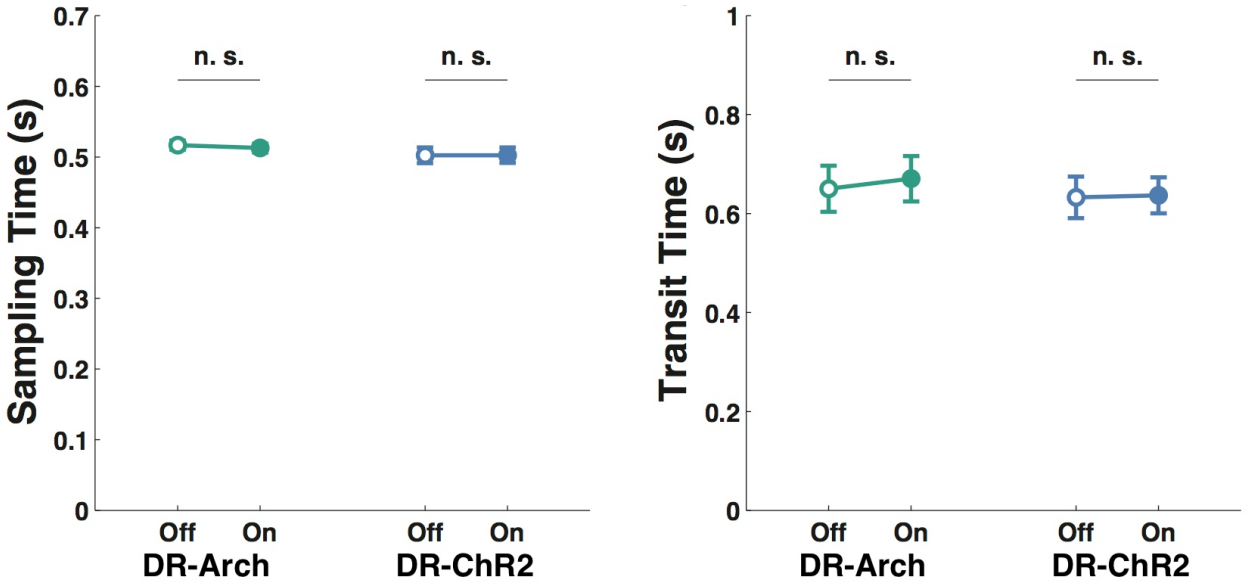






Xu *et al* (2017)

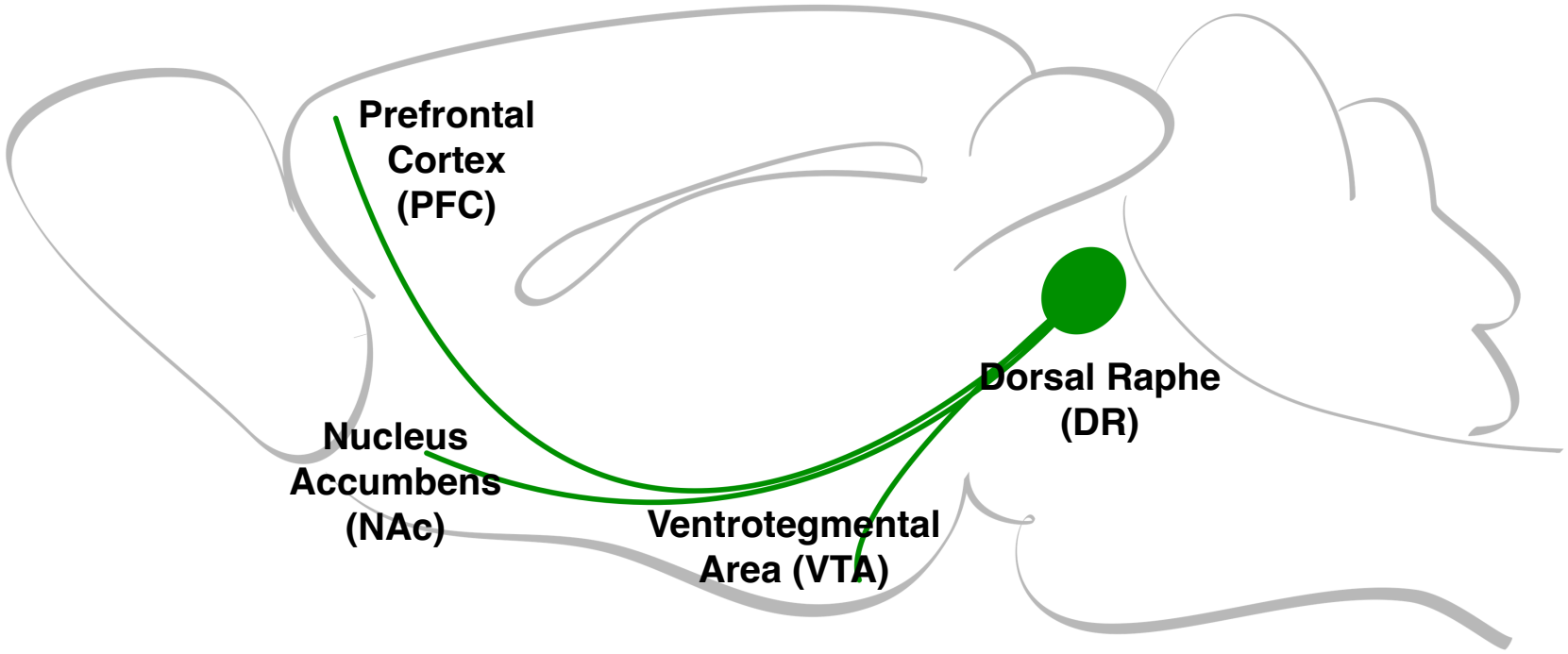
Sampling Time and Transit Time in Task are not Modulated by DR Optogenetic Manipulations



Xu *et al* (2017)

Part 3
NAcSh as a Possible Target Structure

Projection Areas of DR Serotonergic Neurons



The Involvement of Nucleus Accumbens in Intertemporal Choice

Microstimulation

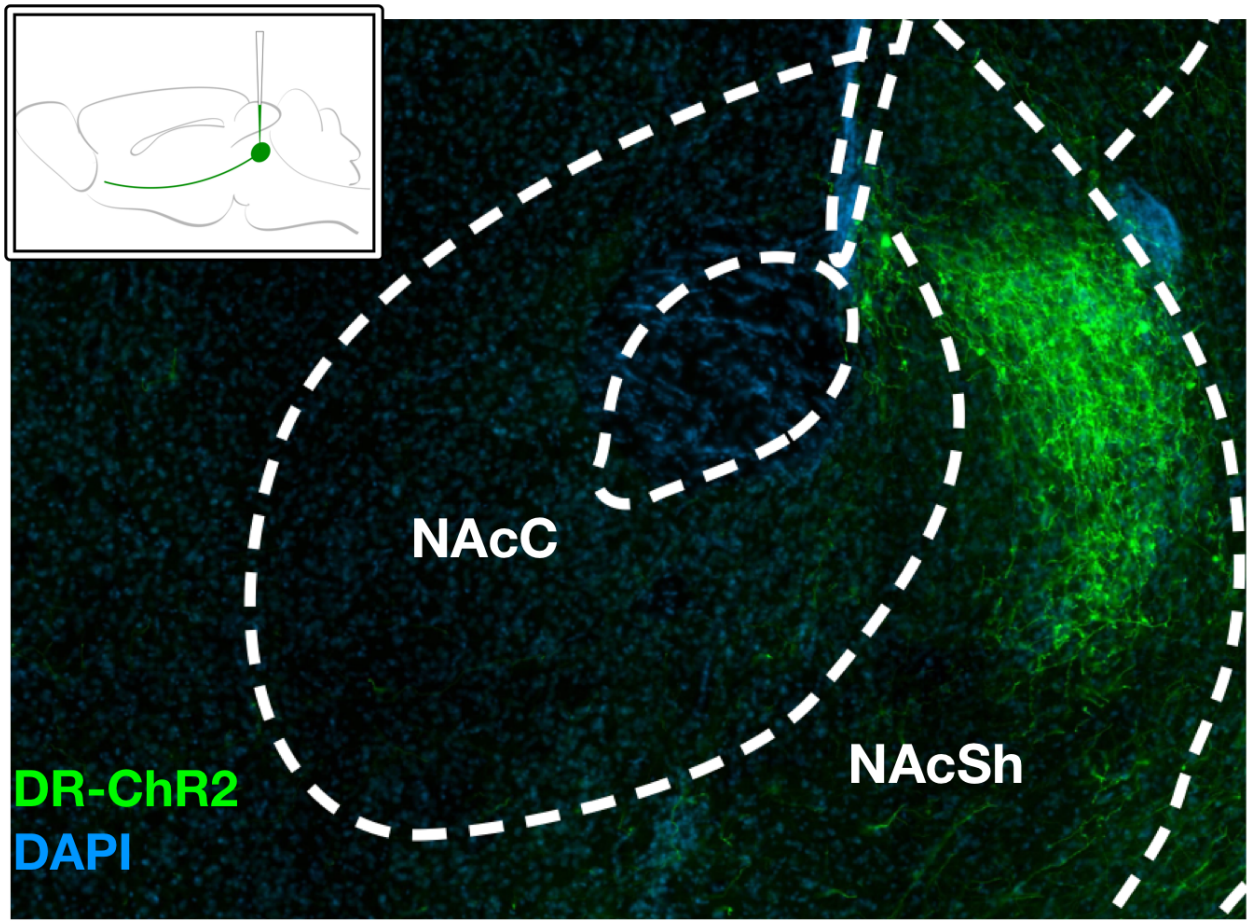
Lesions

Serotonin and dopamine in NAc

VS Activity in fMRI

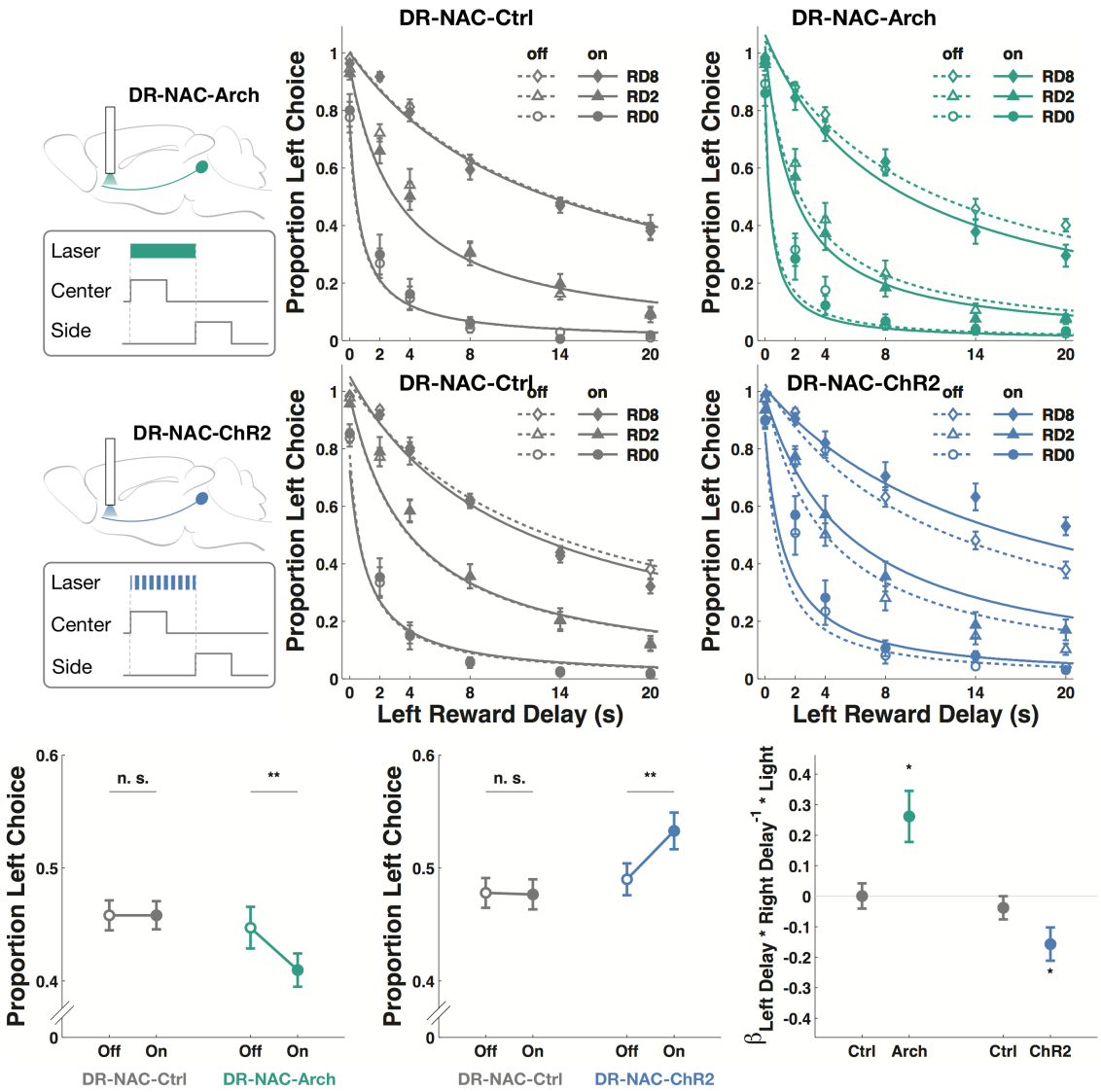
Cardinal et al. 2001, Pothuizen et al. 2005, Winstanley et al. 2005, Hariri et al. 2006, Acheson et al. 2006, Dalley et al. 2007, Schweighofer et al. 2008, Sesia et al. 2008, Wittmann et al. 2010, Dalley et al. 2011

Anterograde Tracing of DR projections in Nac



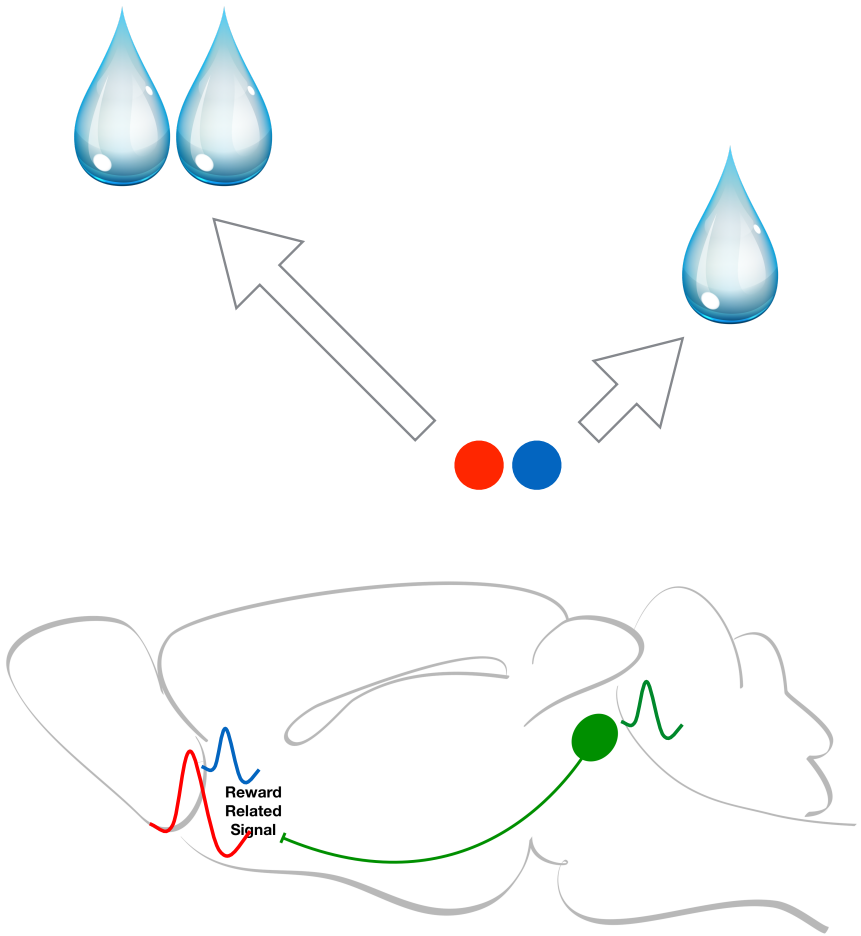
Xu *et al* (2017)

DR Serotonin Projections in NAc Controls Intertemporal Choice



Xu *et al* (2017)

DR 5-HT Neurons Resolve Decision Dilemma?



Acknowledgement

Principle Investigator: Susumu Tonegawa

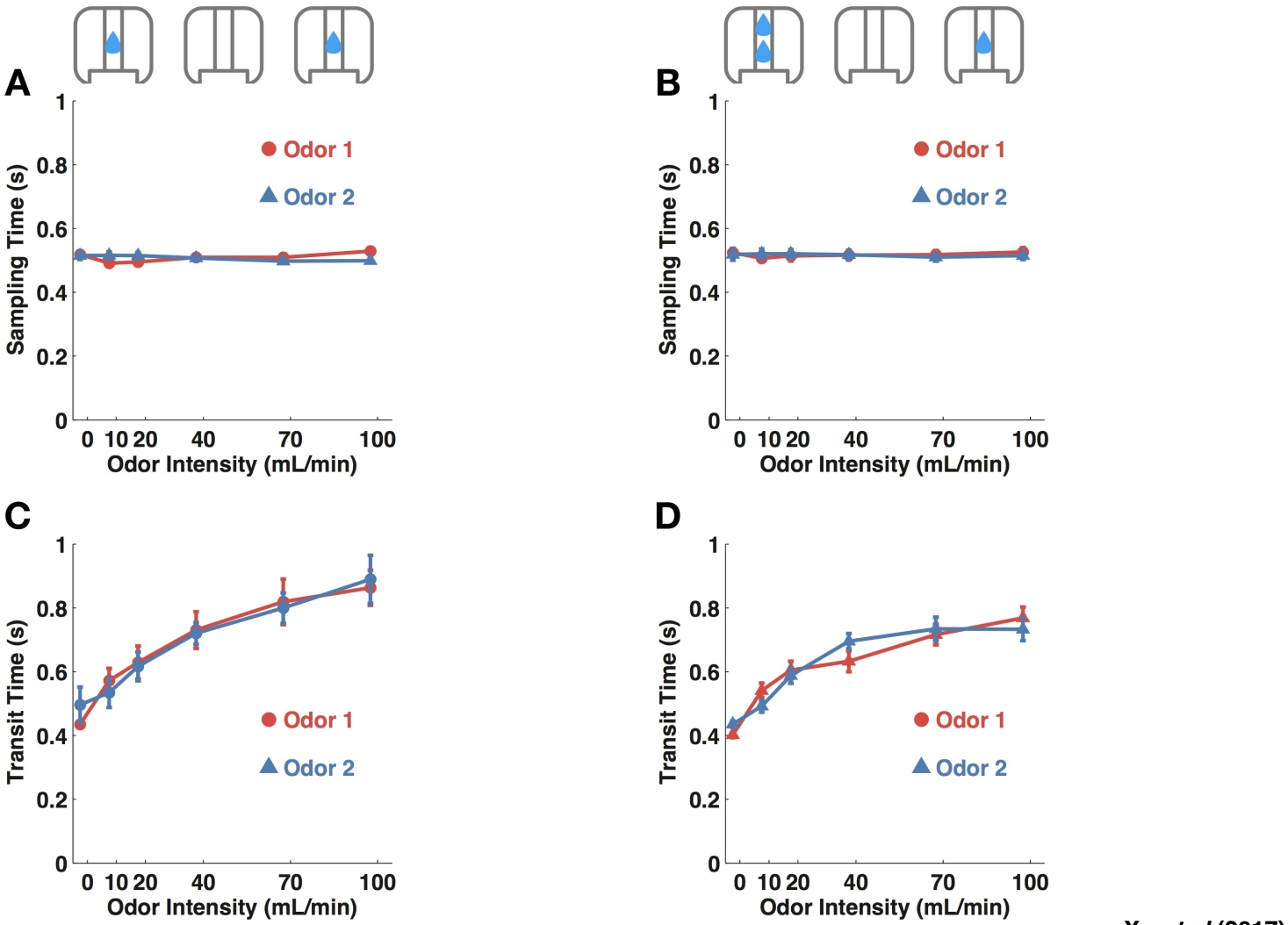
Collaborators: Tim O'connor, Emily Hueske, Gishnu Das, Kean Bustamante

Discussions: Nao Uchida, Earl Miller, Michale Fee

Technical Assistance: Chanel Lovett, Carl A. Twiss

Dorsal raphe serotonergic neurons control intertemporal choice under trade-off
S Xu, G Das, E Hueske, S Tonegawa Current Biology (2017)

Sampling Time and Transit Time are Similar between Odors



Xu *et al* (2017)