



Redefining Drug Discovery Through Innovation

Preclinical Tests For Depression

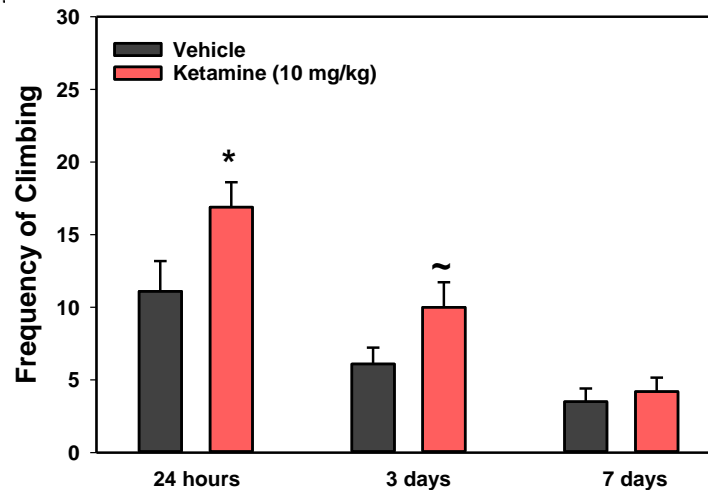
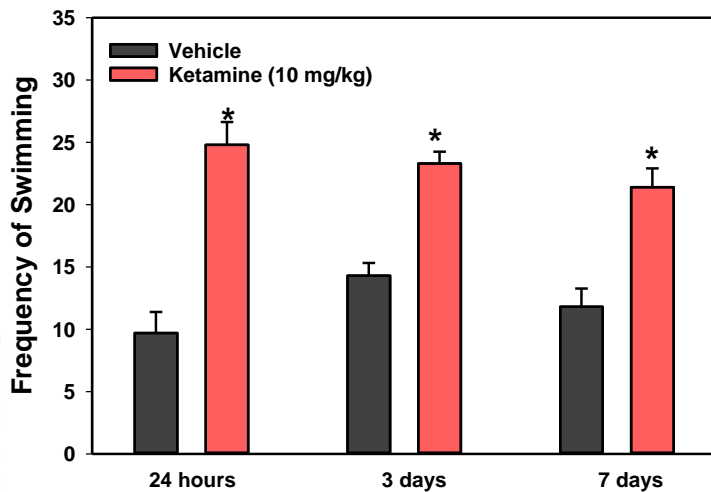
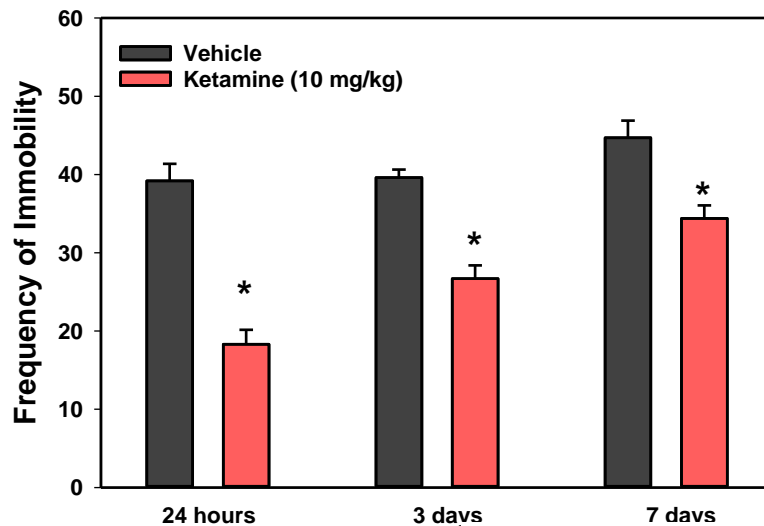
Forced Swim Test

- When rats or mice are forced to swim in a deep cylinder with tepid water they become nearly immobile and cease trying to escape.
- Immobility is thought to reflect a state of “behavioral despair” and is reduced when rats and mice are treated with a wide variety of antidepressants.
- Rodent models of depression are mainly based on predictive validity, objectivity of measured response and their high reliability and reproducibility.



Ketamine Shows a Prolonged Effect in the Rat FS test

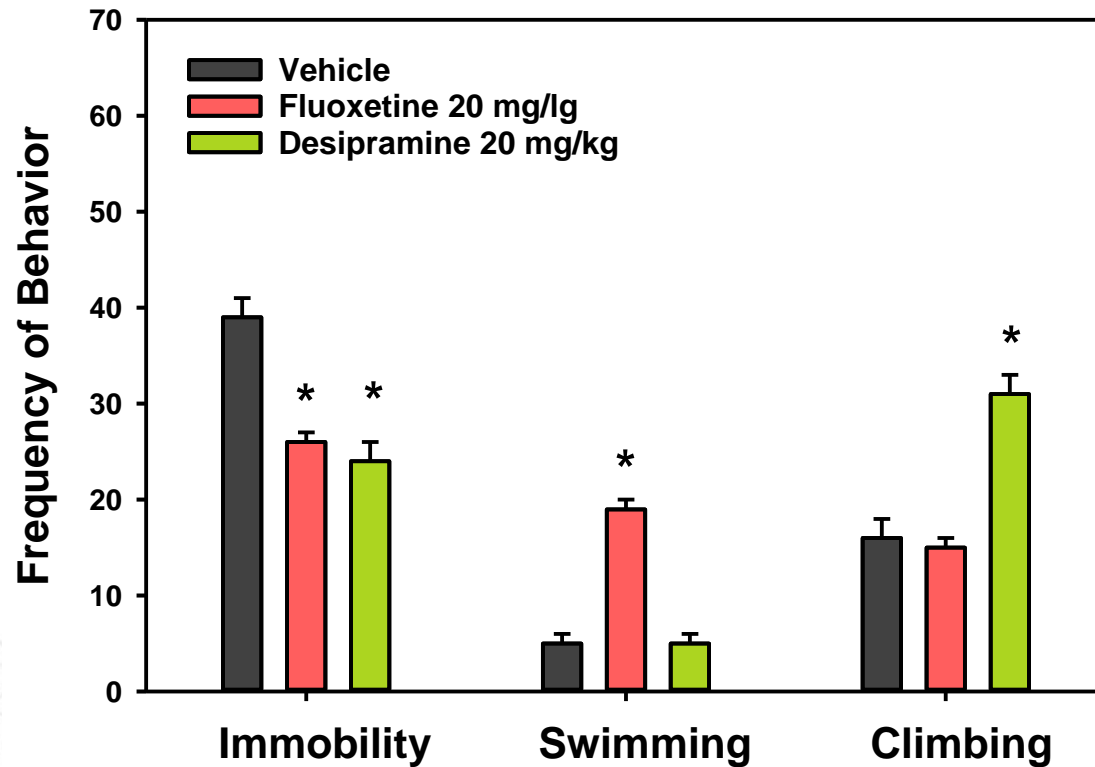
- Single injection of ketamine (10 mg/kg ip) after habituation session produces a long-lasting antidepressant-like effects in SD rats in the FS test



* $p < 0.05$
~ $p < 0.1$

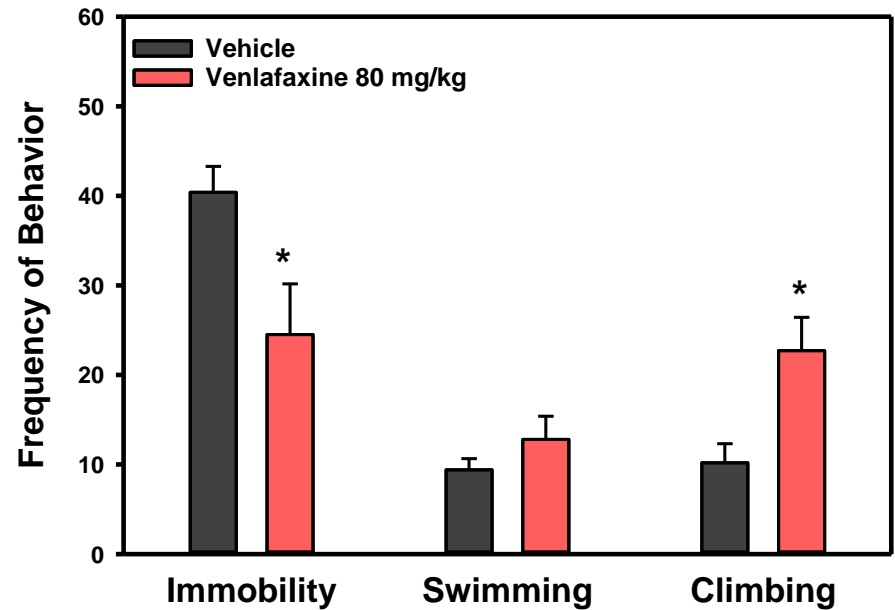
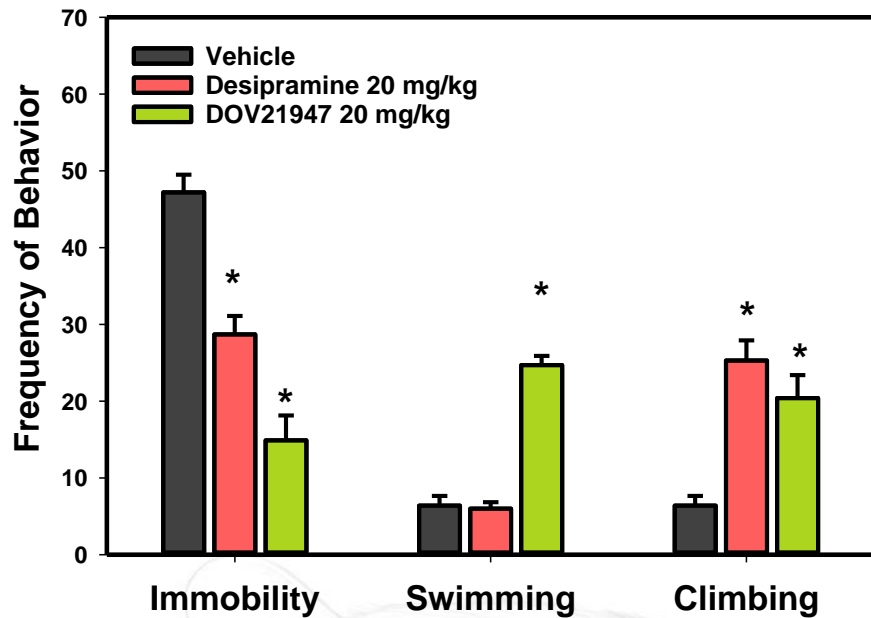
Effects of SSRI and Tricyclic Antidepressants

- The FS test in rats can differentiate between SSRI and Tricyclic-like antidepressants by their differential effects on climbing and swimming behaviors

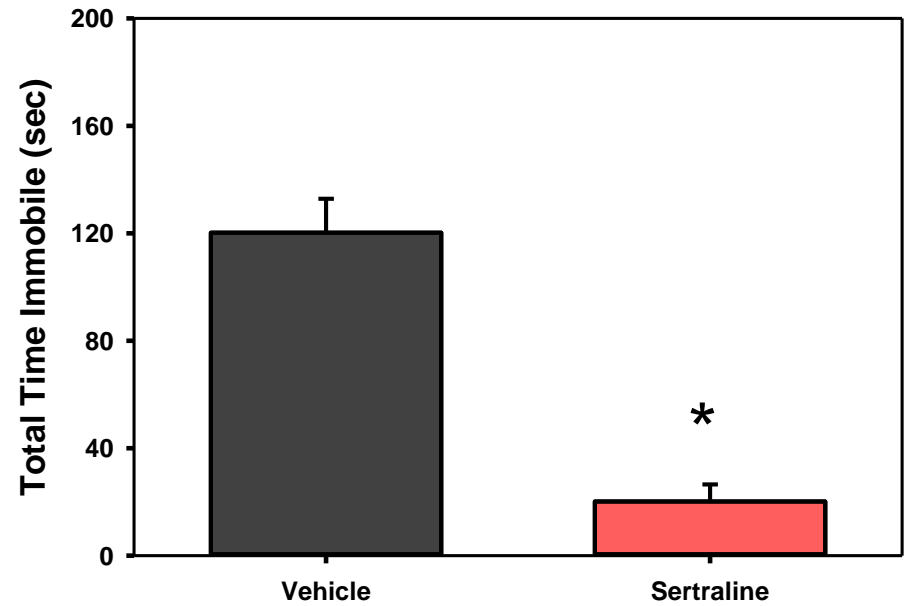
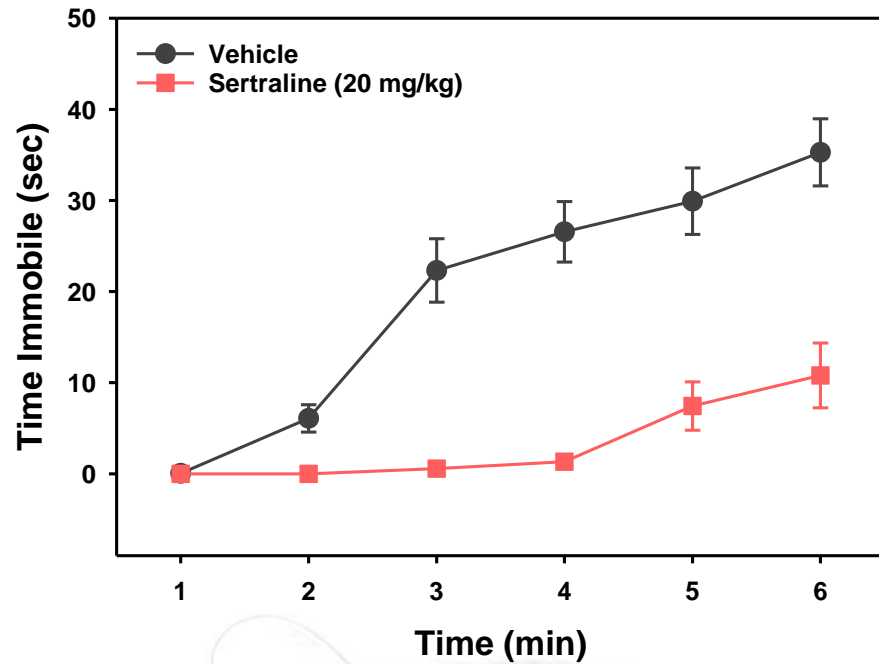


Effects of Double and Triple Reuptake Inhibitors

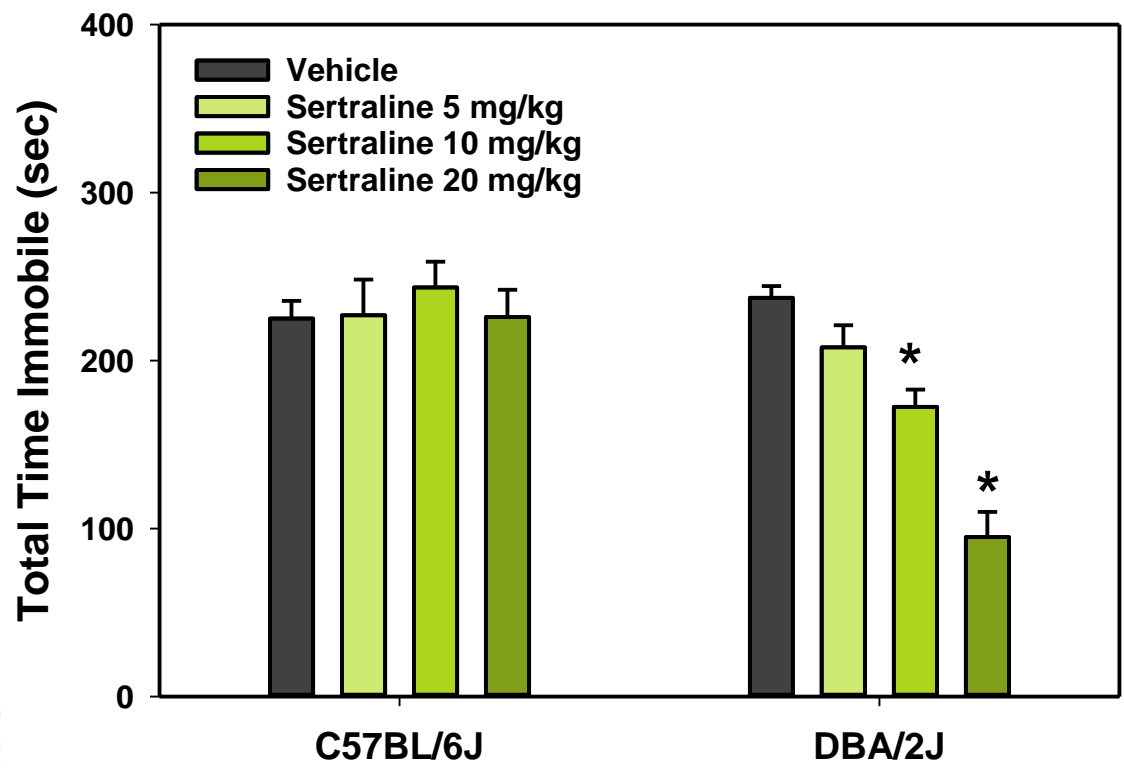
- The triple uptake inhibitor DOV21947 and the 5-HT and NE reuptake inhibitor venlafaxine decreases immobility in the rat FS test.



Sertraline Decreases Time Immobile in Balb/cJ Mice

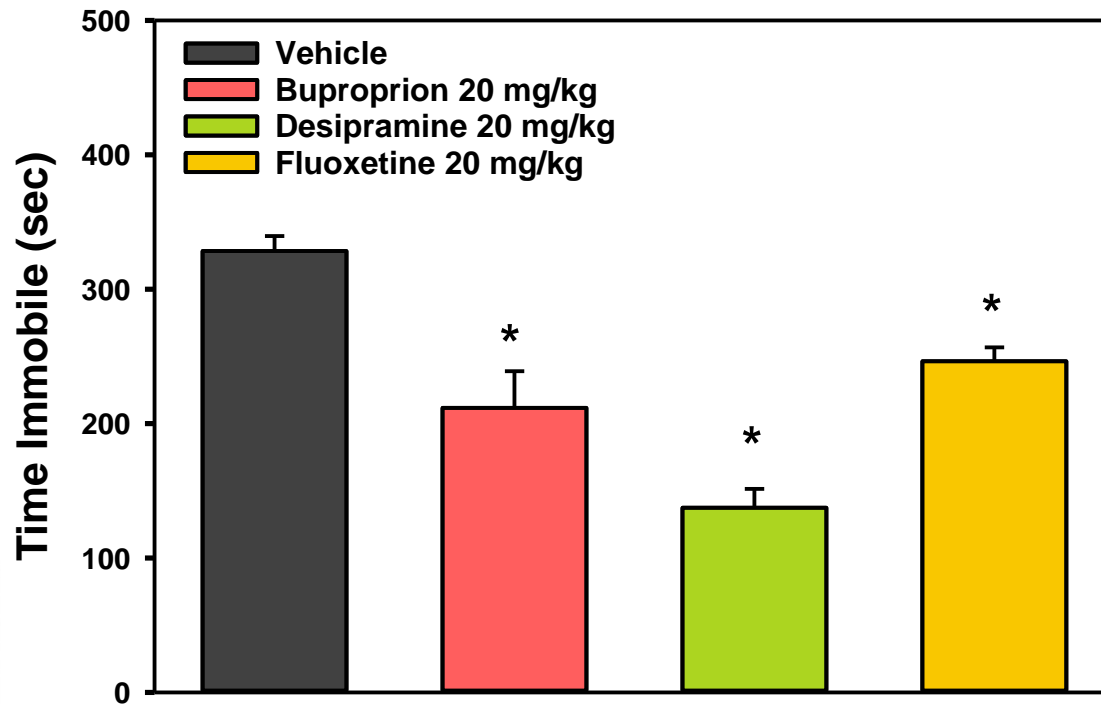


Differential Strain Responses to Sertraline in the FS Test



Tail Suspension in A/J mice

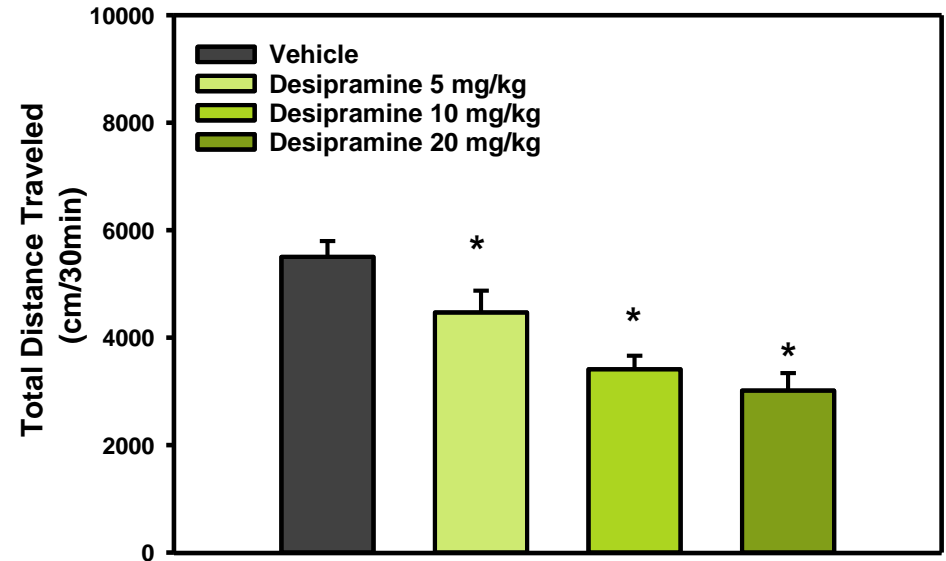
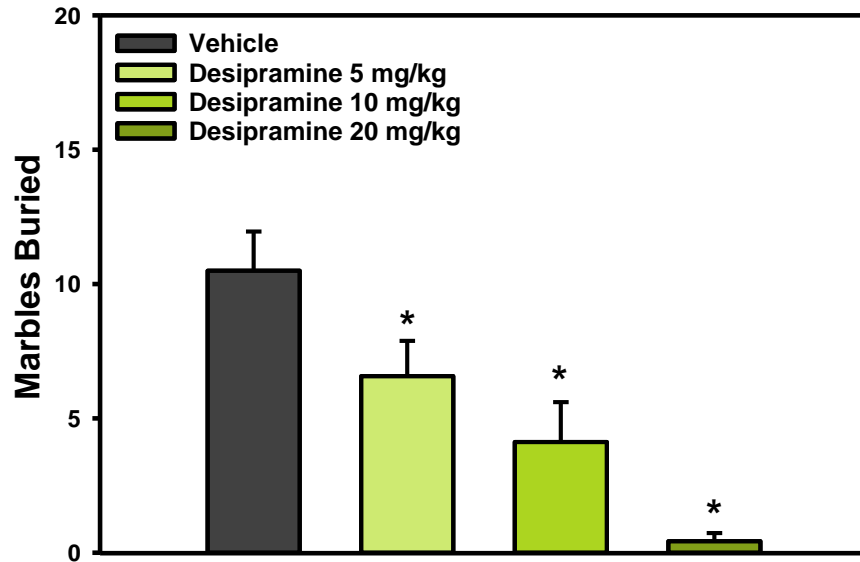
- Mice that are suspended by their tails become motionless.
- Clinically active typical and atypical antidepressants reduces this immobility



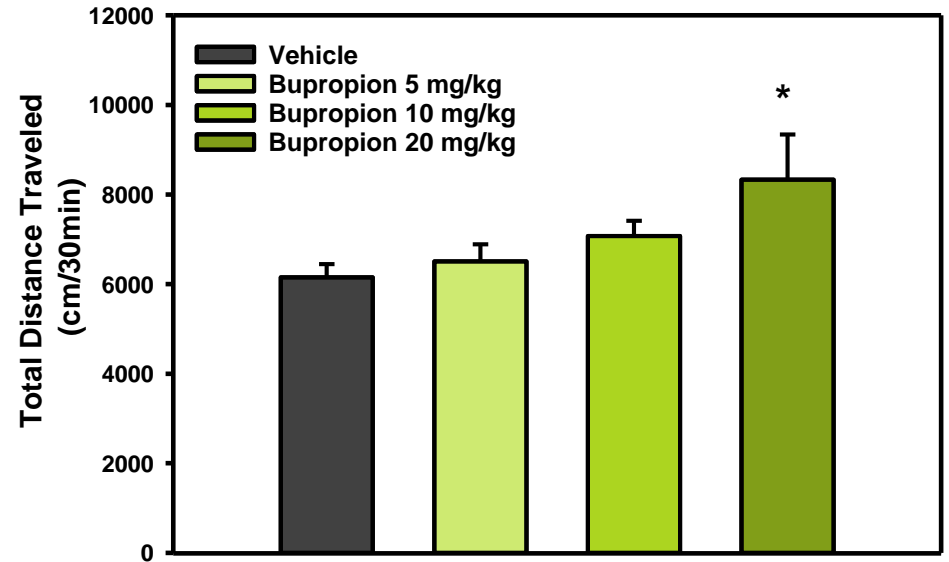
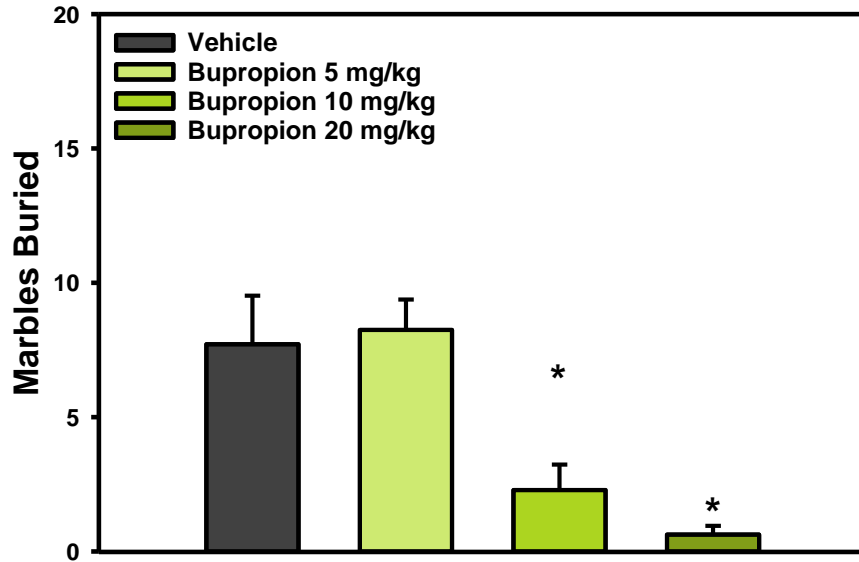
Marble Burying

- Marble burying is normally used as a model for both anxiety and obsessive compulsive disorder.
- Mice are placed individually in clean mouse cages containing approximately 6-cm of hard wood bedding and twenty black marbles placed in spaced rows of 5 for 30 min. Distance traveled during the test is captured by overhead cameras and quantified using Video Tracker Software (ViewPoint Life Sciences, France). After termination of the test the mice are removed from the cage and the number of buried marbles is counted. A marble is considered buried if it is pushed at least two thirds into the bedding.
- This test can be used to investigate pharmacological mechanisms through agonist/antagonists studies. It is also a useful test for yielding surrogate pharmacokinetic information on the duration of action of a drug.
- Mice pretreated antidepressants of various classes show less marble burying ability compared to the control mice

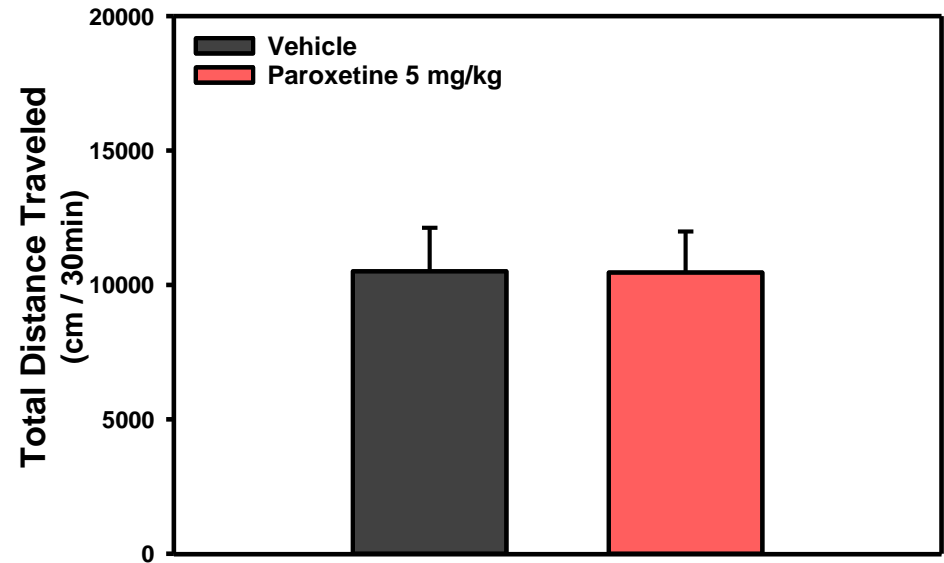
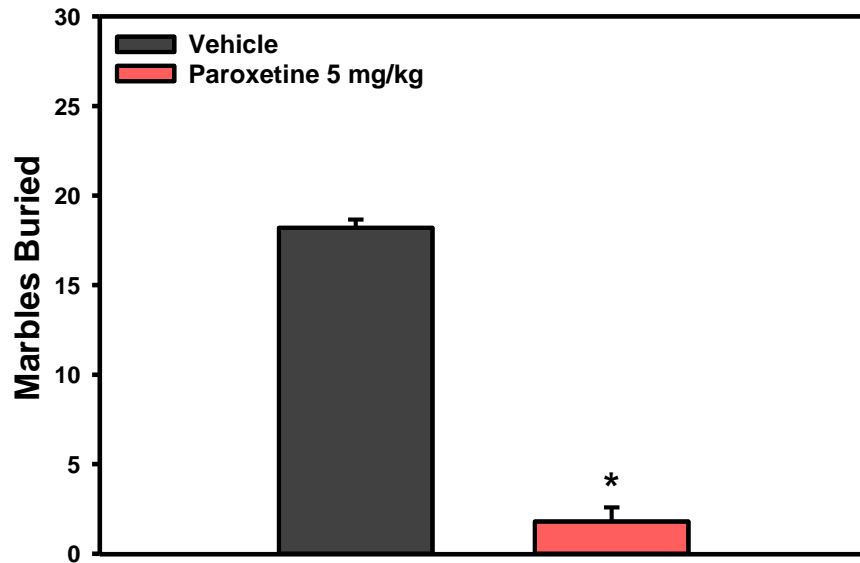
Desipramine Decreases Marble Burying



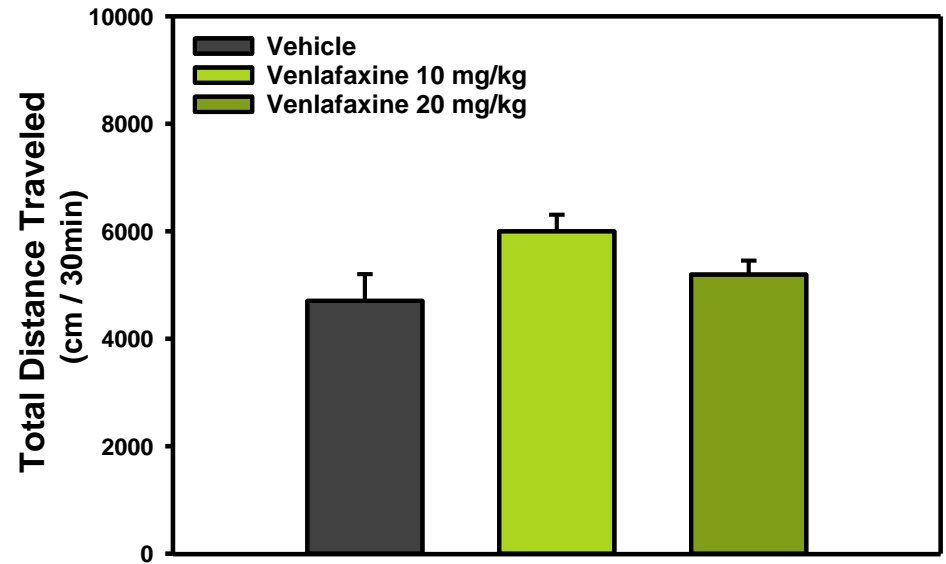
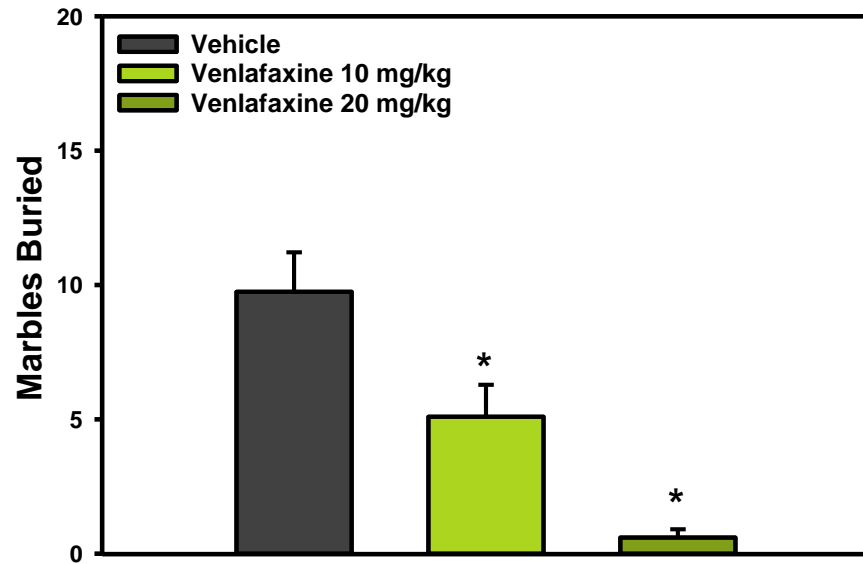
Bupropion Decreases Marble Burying



Paroxetine Decreases Marble Burying

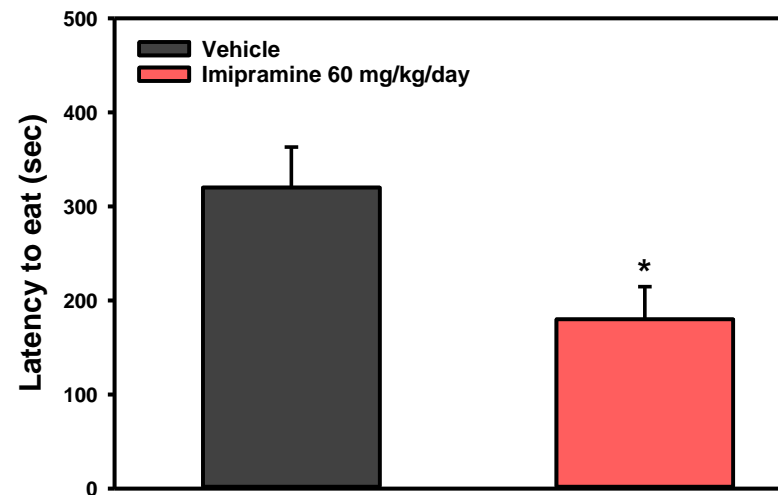
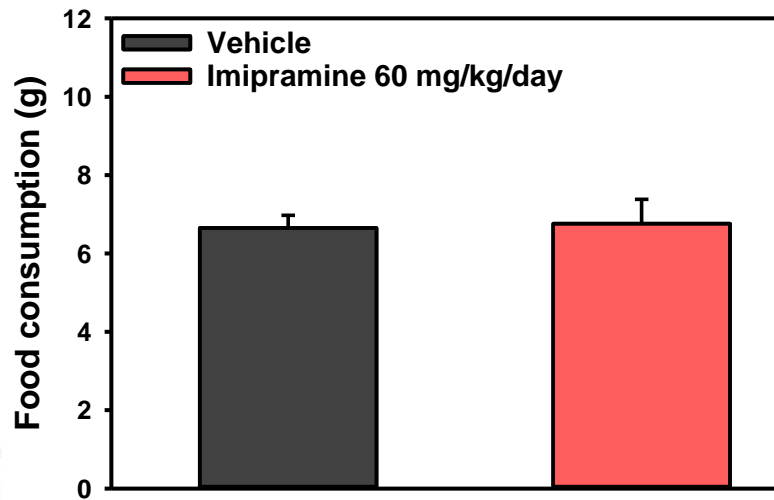
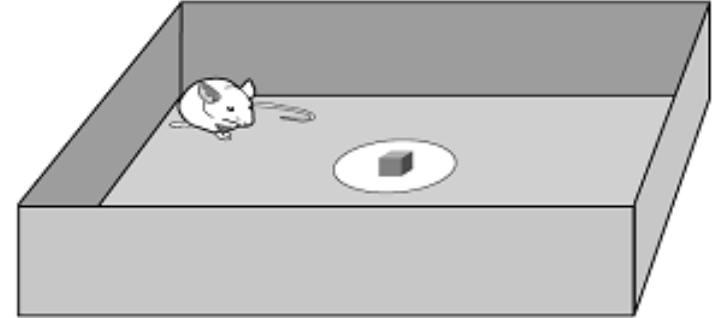


Venlafaxine Decreases Marble Burying



Novelty Suppressed Feeding

- NSF measures a rodent's aversion to eating in a novel environment.
- Chronic administration of imipramine decreases the latency to eat but does not impact home cage food consumption

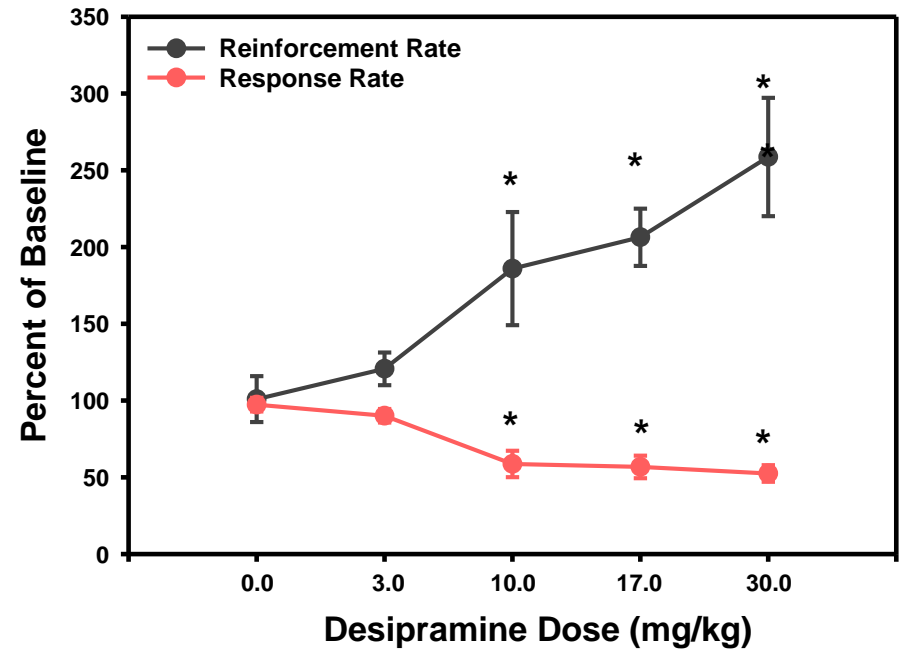
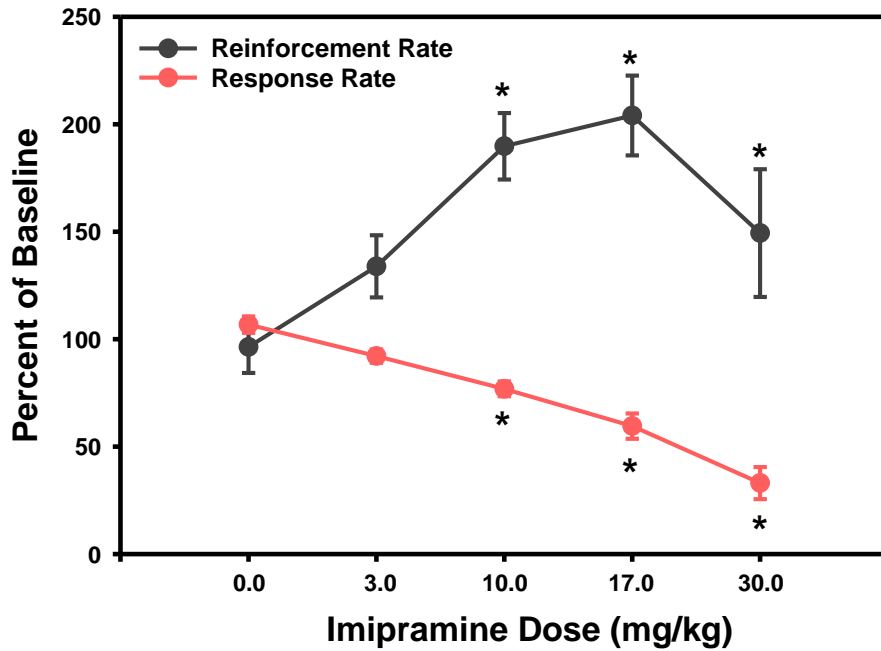


Differential Reinforcement of Low Rate – 72 second schedule

- Differential reinforcement of low rates of responding (DRL) is an operant test that requires behavioral suppression: the withholding of a response for a period of time such as 72 seconds ('DRL72s').
- DRL72s has predictive validity for antidepressant drugs. Administration of different classes of antidepressant (tricyclics, MAOIs, SSRIs) results in a decrease in response rate and an increase in reinforcement rate.
- Non-antidepressant drugs have different profiles of effects, such as, psychostimulants, which increase lever-presses and decrease reinforcers earned.

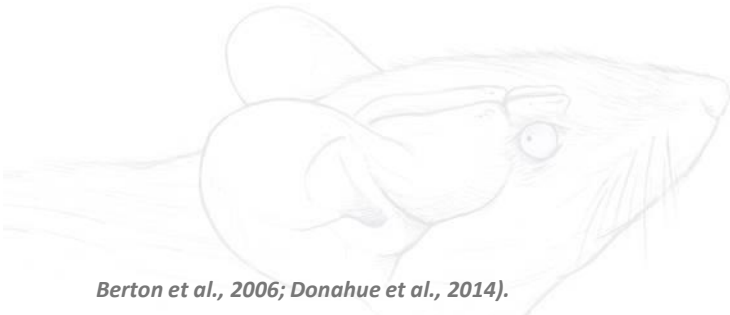


Tricyclic antidepressants increase the reinforcement rate and decrease the response rate



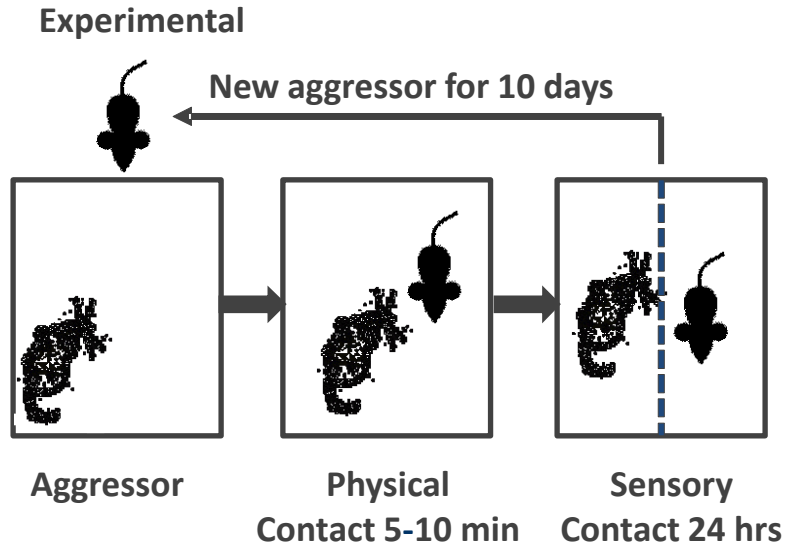
Chronic Social Defeat Stress (CSDS)

- Closely mimics the dynamic range of reactions that an individual can show in response to physical and psychological stressors.
- Ranges from the development of a major depressive disorder, post-traumatic stress disorder or resiliency to these disease states.
- Individual responses to stressors are particularly useful in modeling aspects of anxiety disorders such as PTSD with high construct, face, discriminative and predictive validity

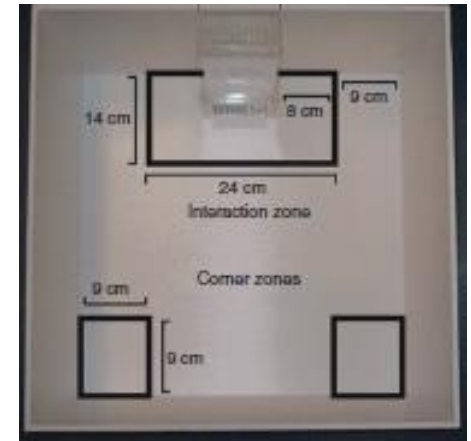


Berton et al., 2006; Donahue et al., 2014).

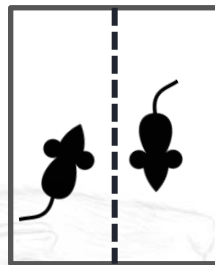
Schematic of CSDS Test



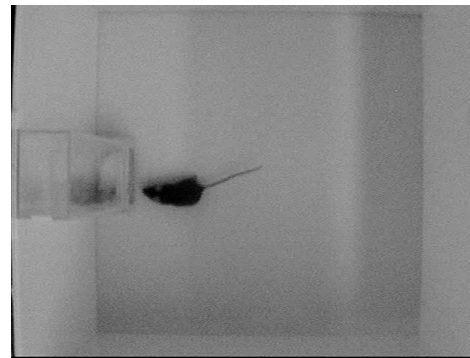
Social Interaction



Control group goes through 24 hr sensory contact with same strain mouse



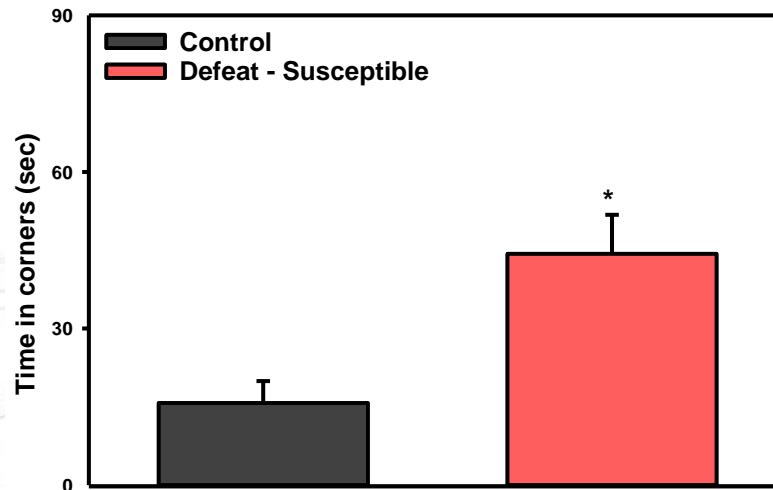
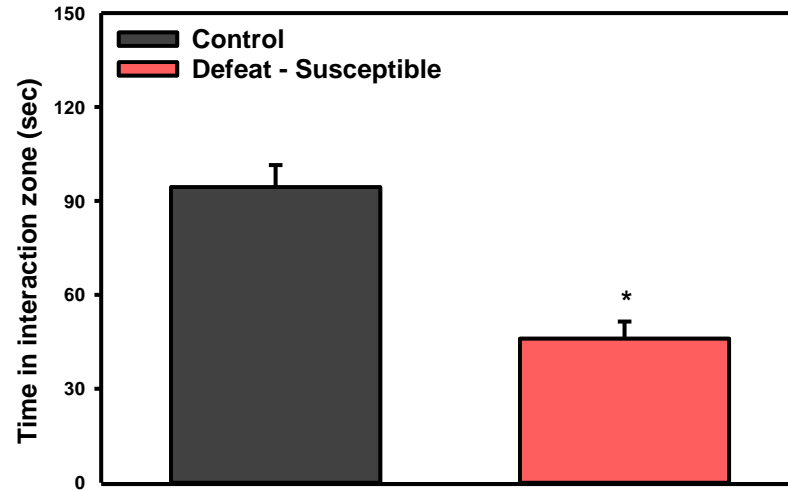
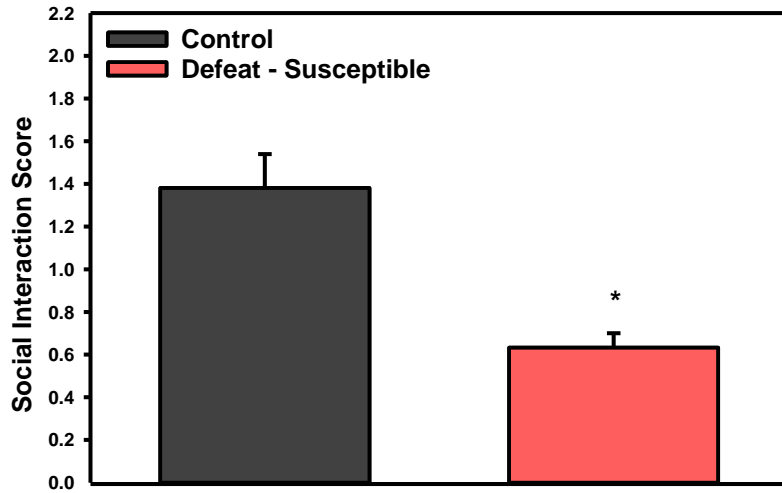
Control



Defeat

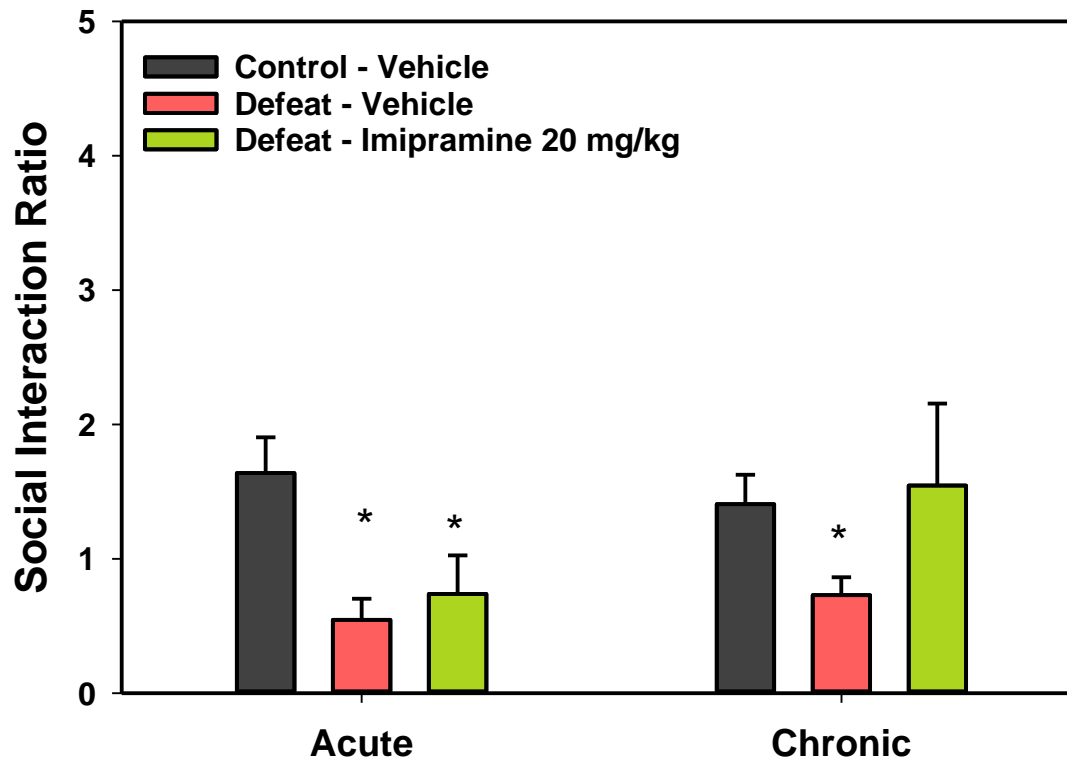


CSDS – Control and Defeat Phenotype

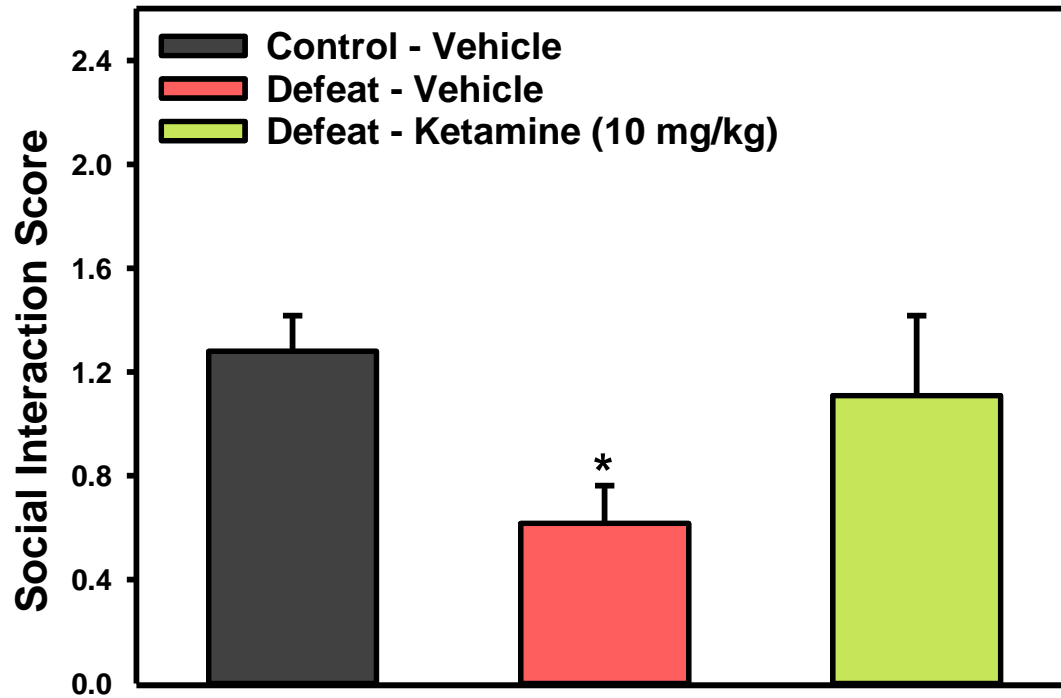


Effects of Imipramine on Social Deficits in Defeated Mice

- Oral administration of imipramine for 2 weeks attenuated social deficits in defeated mice.
- Acute administration of imipramine does not show efficacy in this model



Ketamine Attenuates Social Deficits in Defeated Mice



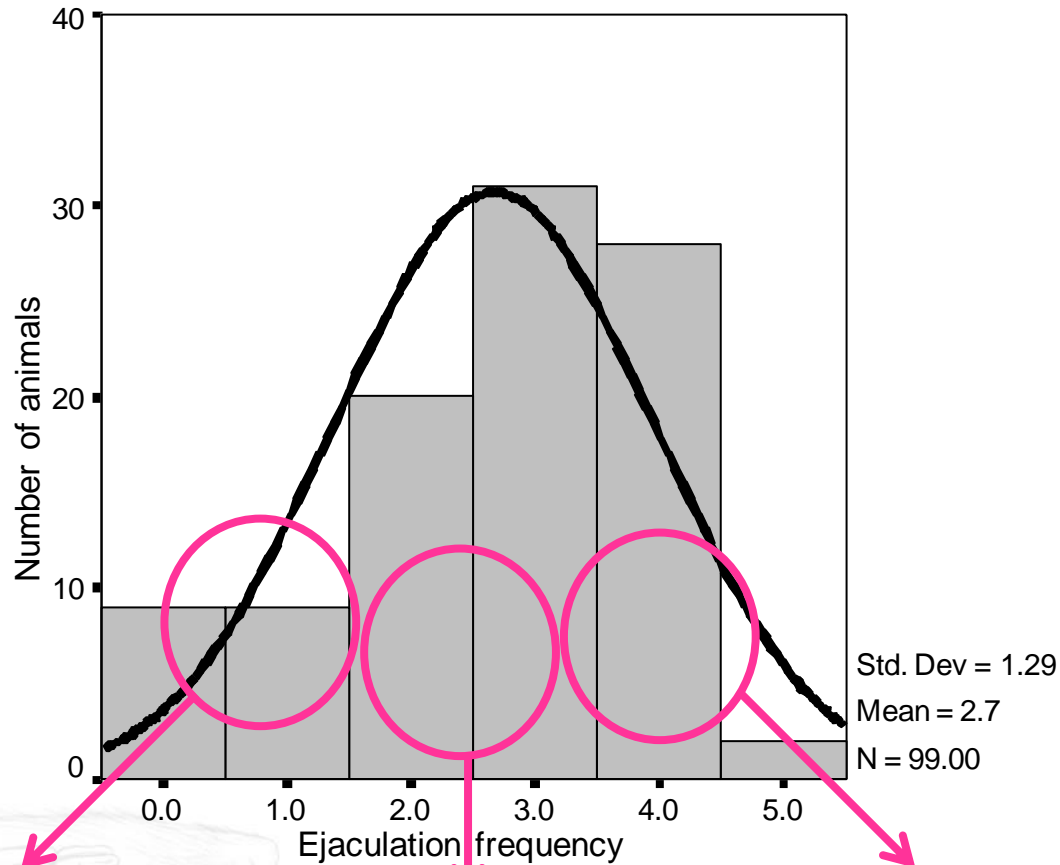


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Sexual Dysfunction in Rats



Normal distribution of ejaculation frequency during 30min exposure to receptive female

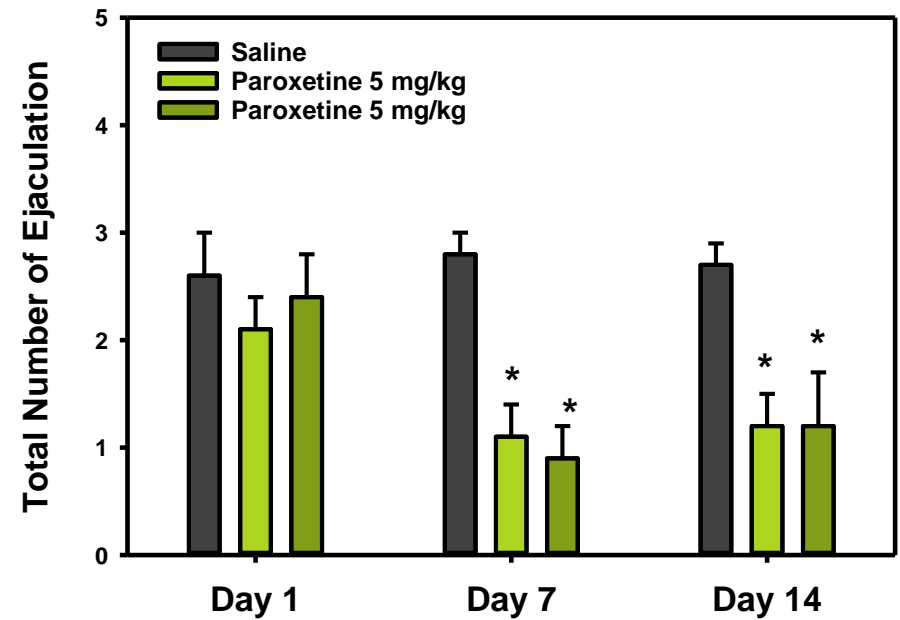
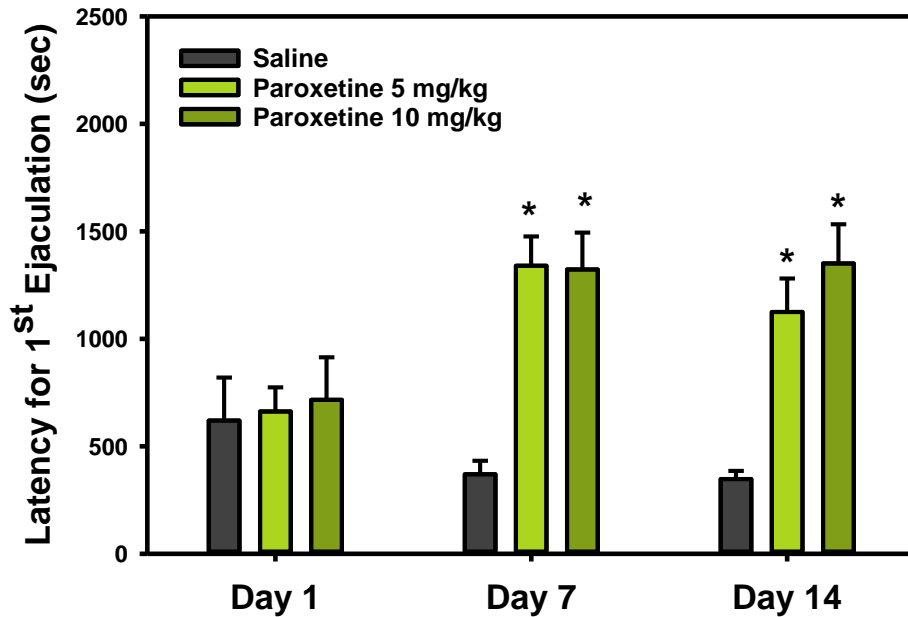


**'delayed' ejaculation
(n=12)**

**'normal' ejaculation
(n=12)**

**'rapid' ejaculation
(n=12)**

Chronic Administration of Paroxetine Causes Sexual Dysfunction



Effects of Bupropion on Sexual Function

