

# ANXIETY-LIKE BEHAVIOR DURING ABSTINENCE FROM COCAINE EXPOSURE IN RATS

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## Introduction

- Relapse is a manifestation of cocaine induced craving and/or abhorrent affect (i.e. anxiety or depression) during bouts of abstinence.
- Our laboratory is interested in how cocaine-use induces neural adaptations that mediate changes in motivation and affect during abstinence.
- We developed a rat model of cocaine exposure and in this study determined whether it induced a change in affect (i.e., anxiety-like behavior) during the first week of abstinence.

- Related studies report anxiety-like behavior during the first 3 days of abstinence from cocaine exposure using apparently similar designs and procedures (Harris et al., 1993; Sarnvai et al., 1995).

- **Hypothesis: Exposure to repeated escalating doses of cocaine increases anxiety-like behavior in rats during a brief period (i.e., 1 week) of withdrawal from cocaine.**

- The shock prod defensive withdrawal test (Treit et al., 1981) was used to characterize the rats level of anxiety. The *primary hypothesis* was that the cocaine exposure regimen would induce an increase in burying behaviors on one or more days during the first week of withdrawal.

- However, the analysis of burying behavior did not support the primary hypothesis (see Figure 1). But, burying behavior accounted for only 4-5% of the rats' behavior during the observation period.

- We reported here, are secondary analyses that evaluated *other* defensive behaviors: defensive withdrawal (i.e., time spent rearing against the back wall), approach to the previously noxious stimulus (i.e., time spent against the front "stimulus" wall), and locomotor activity (i.e., open cage rearing).

## Methods

Subjects: 224 Long Evans male rats (~250g); Pair-housed under standard lab conditions.

### Procedure and Design:

#### A. See Sequence of Events

#### B. Defensive Burying Test (Pineal et al., 1978)

- Cage mates were shocked sequentially (3-165 sec apart) but observed during the same 10 min period ~30 min after the shock.
- **Shock Order** (1<sup>st</sup> or 2<sup>nd</sup>) was controlled by including this variable in the statistical analysis.
- **Dependent variables for the secondary analysis included**

1. **Far Wall Rearing** (duration),
2. **Front Wall ("prod wall") Rearing** (duration), and
3. **Open cage Rearing** (frequency)

#### C. Operational Definitions:

Rearing: Any instance in which the rat elevated two fore paws and elongated its body vertically to achieve a straight back (not sitting). One instance of rearing ended when a single fore paw returned to the bedding level.

Location of the rear was determined by the orientation of the rats' hips and contact area of the forepaws.

- #### D. Behaviors were scored from video recordings of the behavioral tests by D.D. (primary analysis), D.R.P. & M.A.H. (secondary analysis), and A.C.T. (for the purpose of establishing inter-rater reliability.)

### Data Analysis:

- Preliminary analyses evaluated the possibility that pair housing, differential weight gain among pairs, and/or behavioral response to the shock varied systematically (they do not, see Figure 2 for example).
- Secondary analyses used two-way ANOVA to test for group differences in the expression of each dependent measure.
- Inter-rater reliability (IRR) was established by having the scorer's code similar data (15% of the total) and correlating the data and identifying percent agreement (not shown).

## Sequence of Events

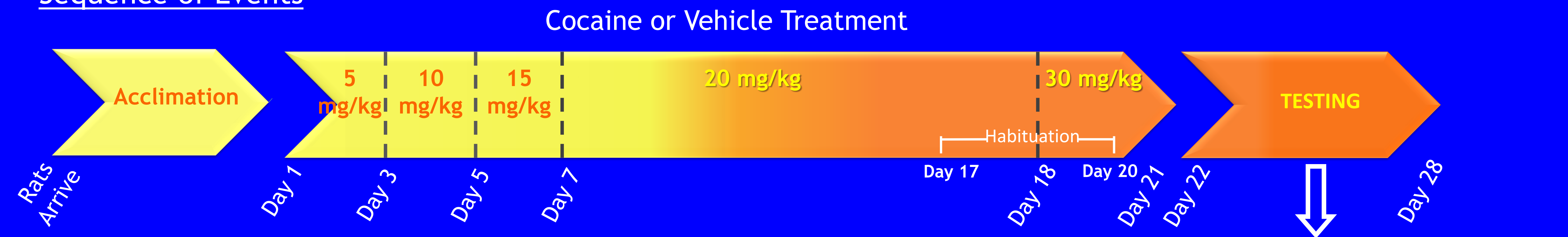
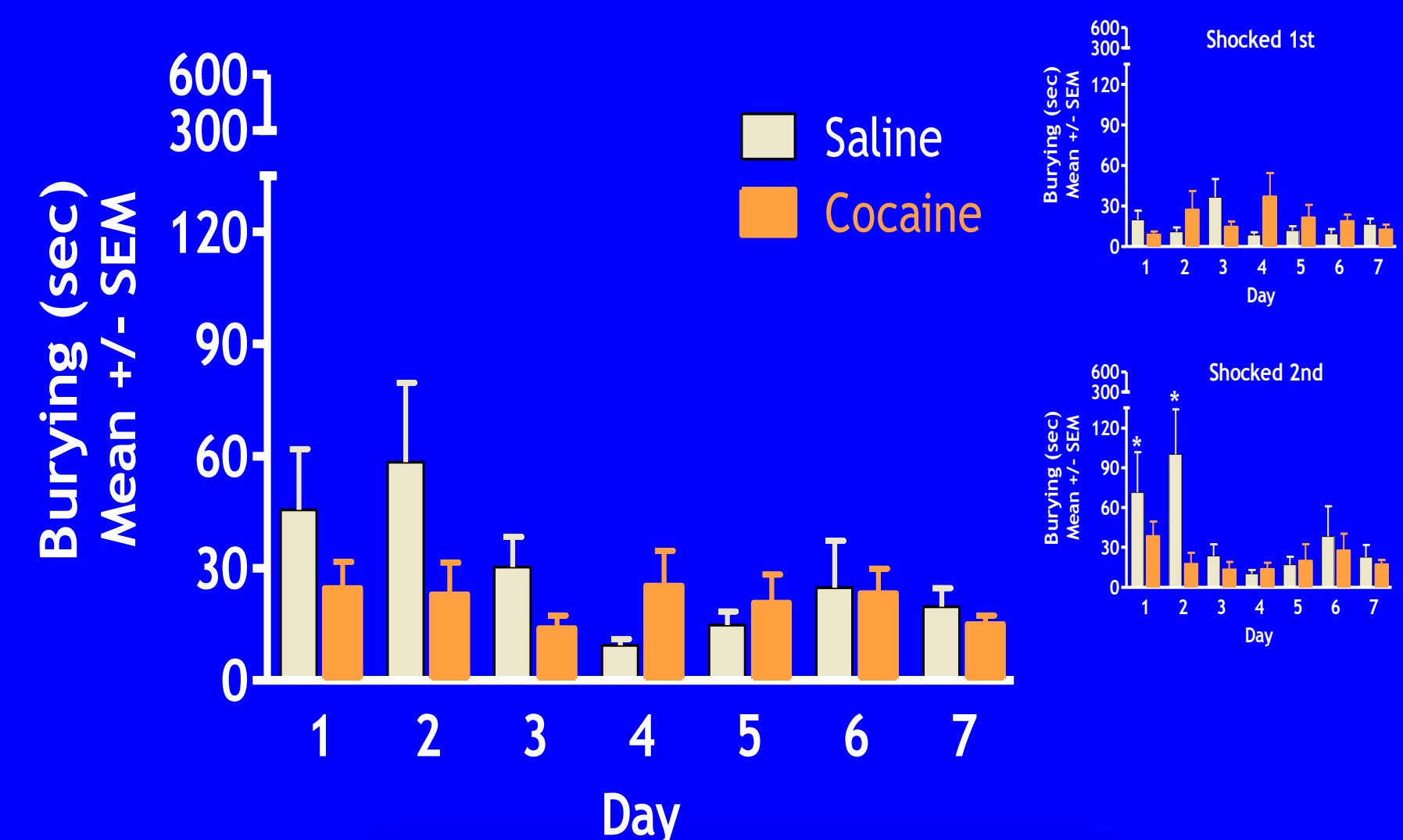
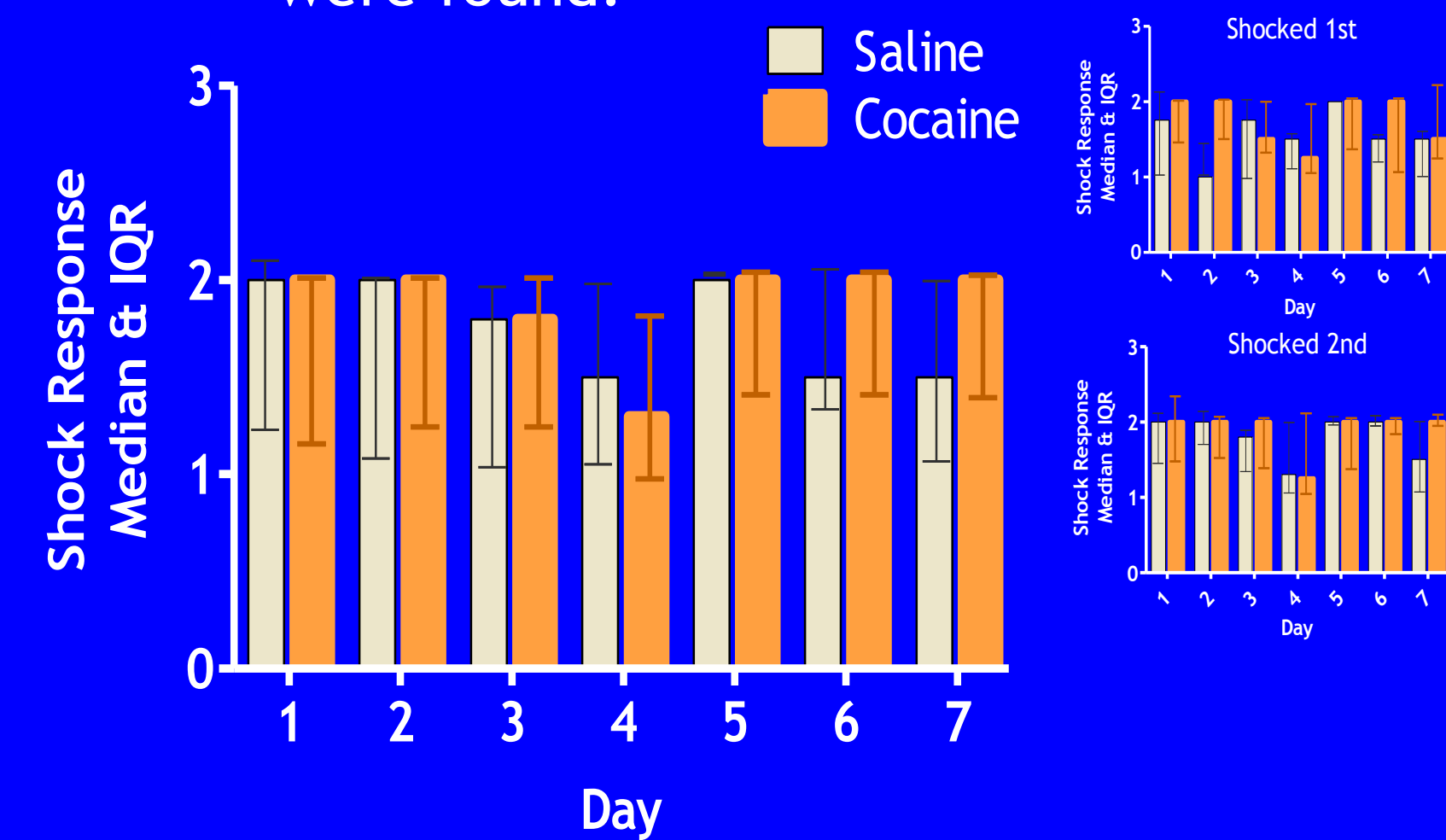


Figure 1: Cocaine treatment did not increase *burying response* during the first week of abstinence



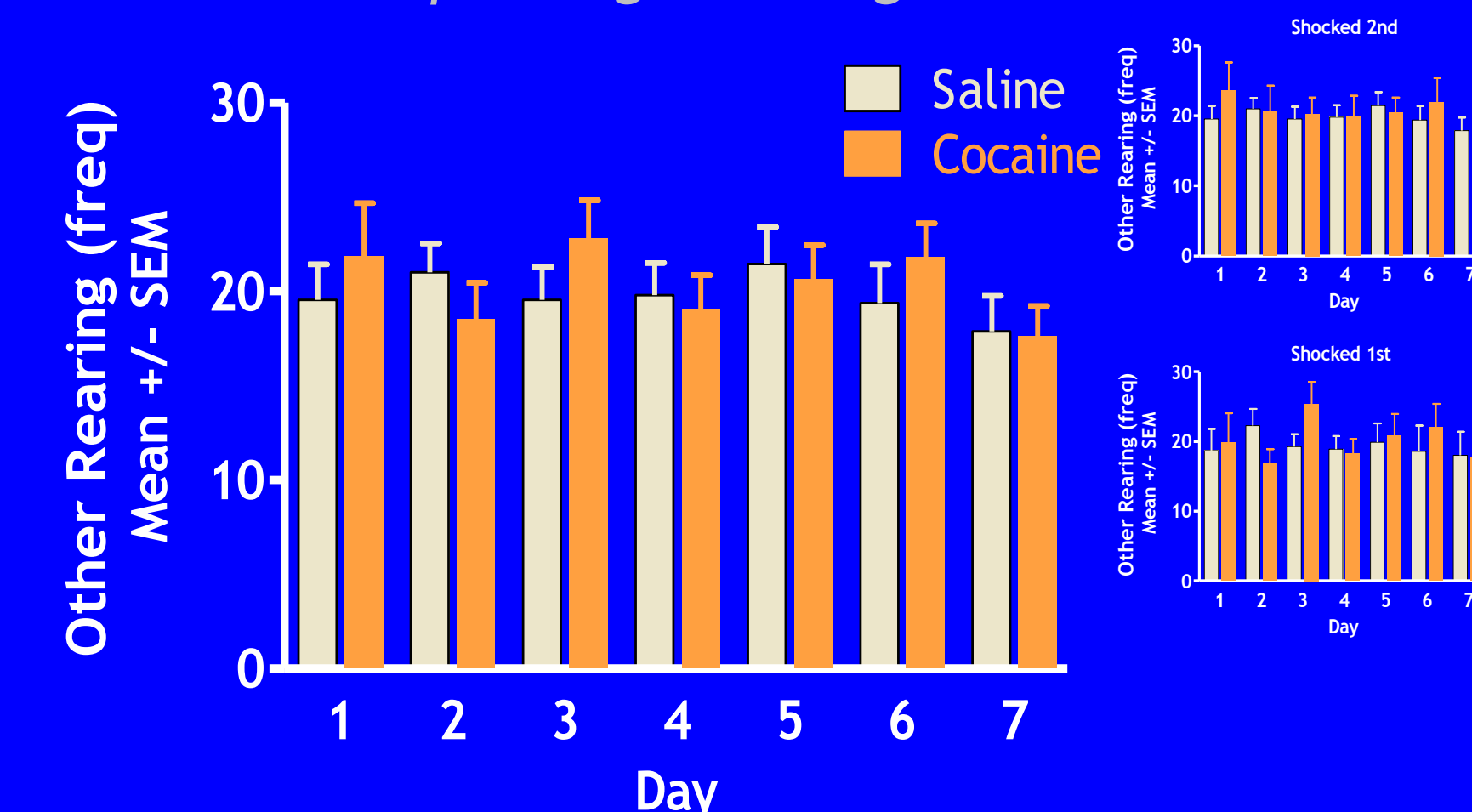
There was a significant 3-way interaction between cocaine history, Day of abstinence and Shock Order. \*  $p < 0.05$  as compared to cocaine treated rats (same day) or saline treated rats day 3,4,5 & 7.

Figure 2: No differences between groups in the behavioral response to the snout/paw shock were found.



Shock responses are the median score assigned by 3 observers blind to the condition of the rat using a ranked or scale. 1= twitch, 2= jump and run, 3= jump and freeze

Figure 5: No group differences in the *frequency of open cage rearing* were observed



## Cocaine or Vehicle Treatment

Figure 3: No differences between groups in time spent at the *far wall rearing* were found.

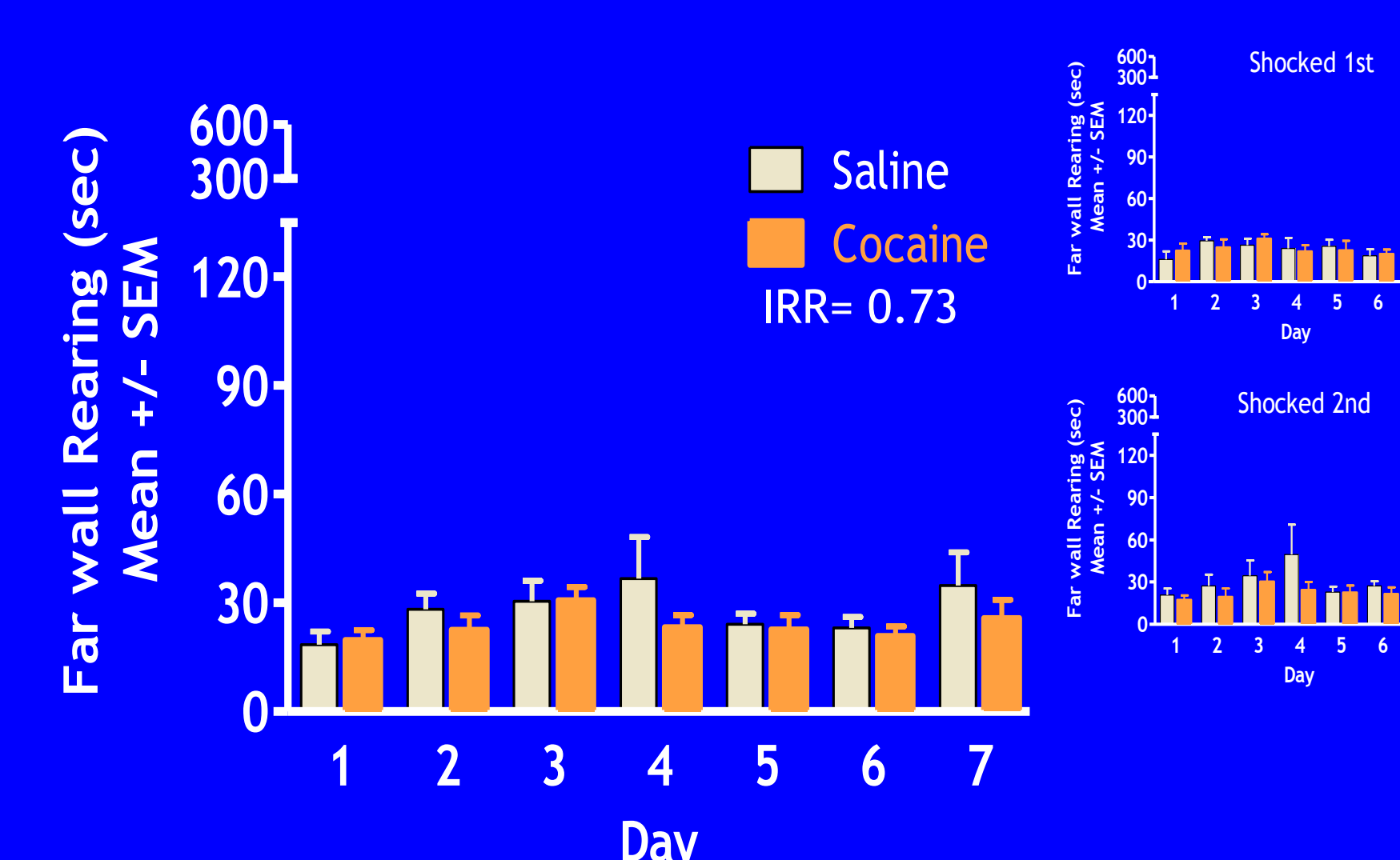
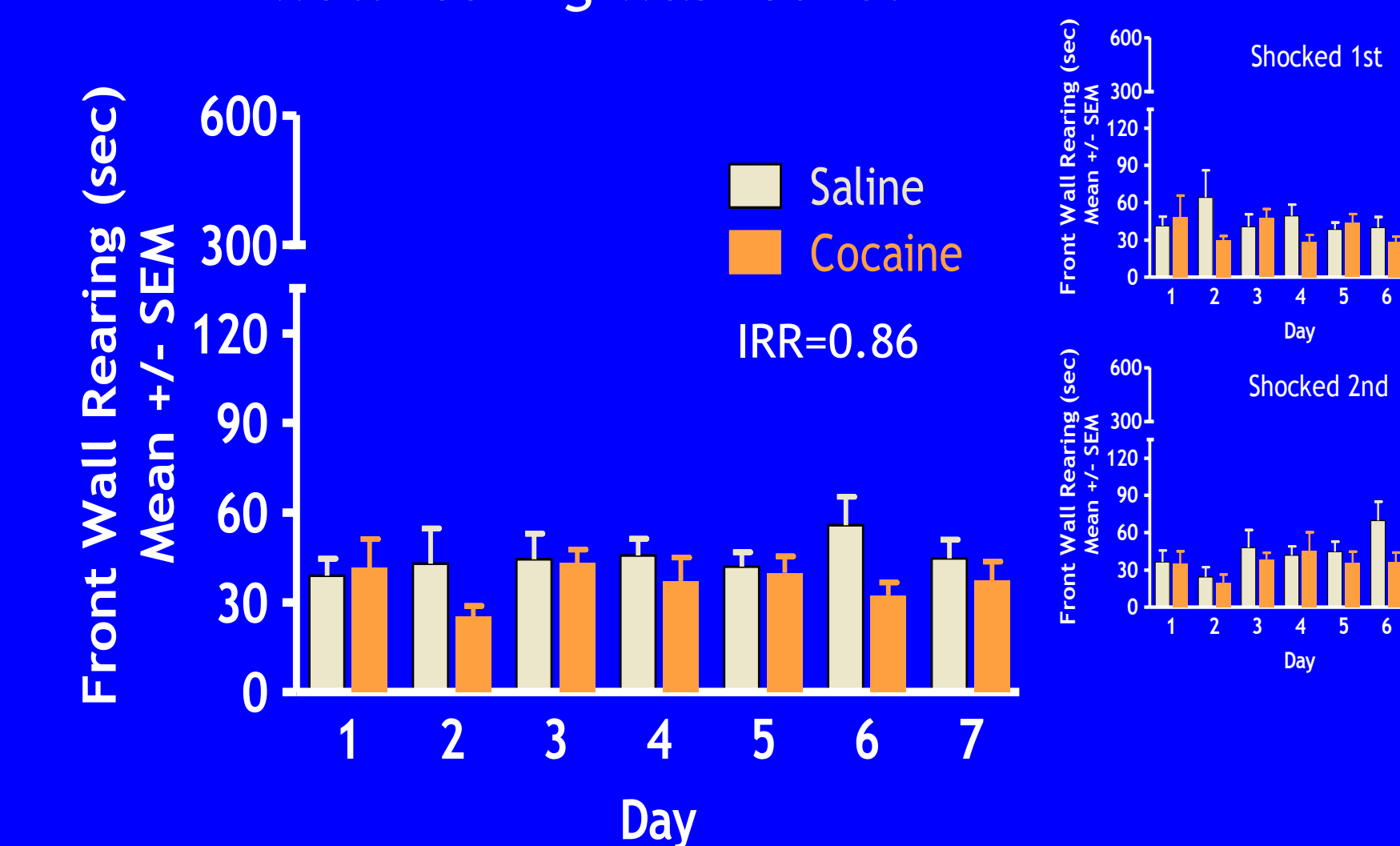
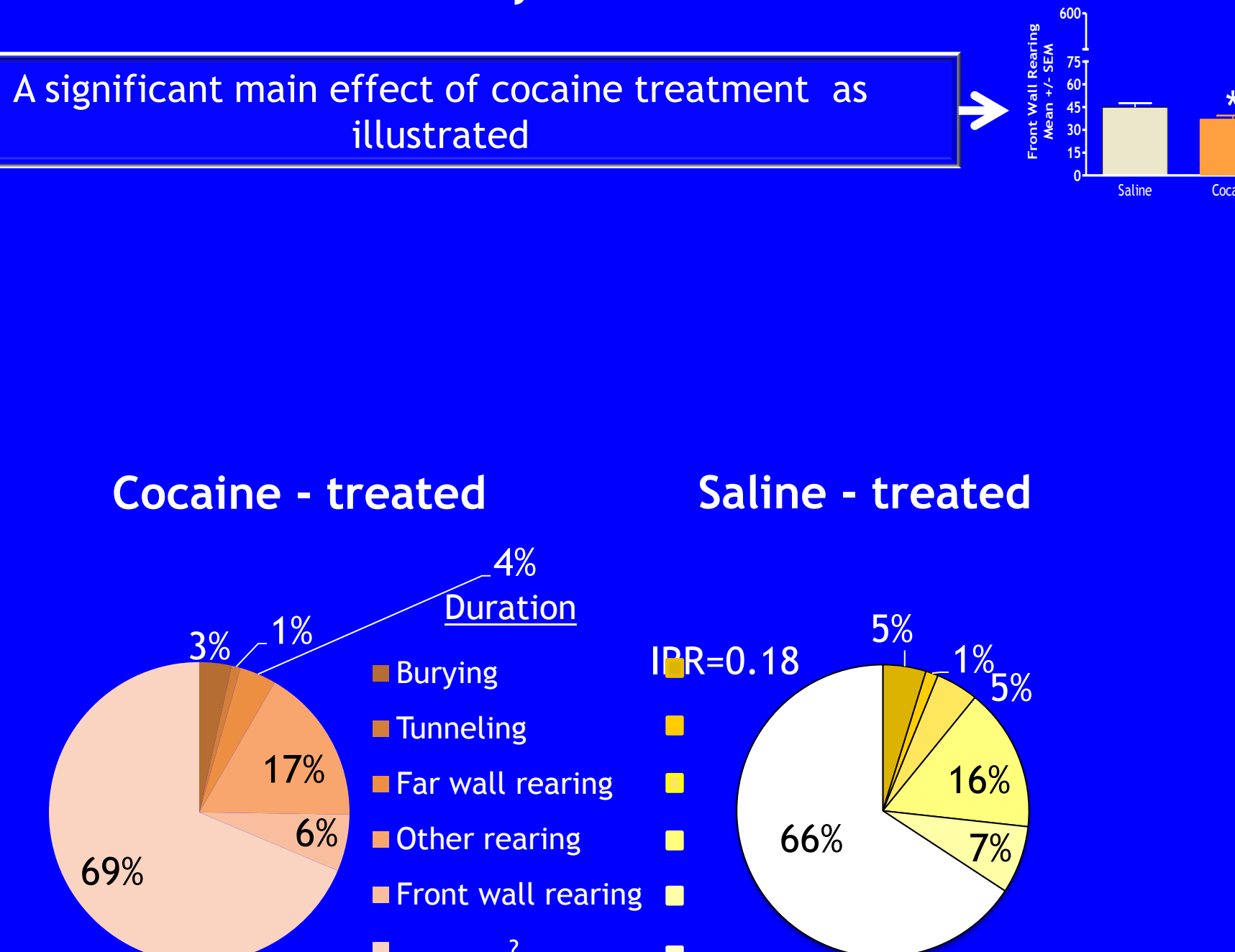


Figure 4: No interaction between cocaine treatment and days of abstinence in time spent in *front wall rearing* was found.



A significant main effect of cocaine treatment as illustrated



## Conclusions

- Prolonged cocaine exposure did not lead to an increase in defensive behavior (i.e., burying behavior or fall wall rearing) over the first week of abstinence. In fact, cocaine exposed rats showed less defensive burying on the first 2 days of abstinence compared to a subset of saline-treated rats.
- Cocaine treated rats showed significantly fewer front wall rears which may suggest a decrease in willingness to approach a noxious stimulus.
- **These results do not support the use of this rat model in the study of the neurobiological mechanisms mediating cocaine-use induced changes in affect during short bouts of abstinence (i.e., anxiety).**
- Methodological differences between studies may point to unrecognized, but important, variables in the manifestation of cocaine-induced changes in anxiety-like behavior, including strain, length of cocaine treatment, total dose, and pattern of exposure
- Our secondary analysis increased the amount of the rat's behavioral repertoire measured during the observation period (2-5x) over the initial analysis, although the behavior expressed in the majority of the observation period remains unmeasured (see pie charts).

## References

- Basso, A. M., Spina, M., Rivier, J., Vale, W., & Koob, G. F. (1999). Corticotropin-releasing factor antagonist attenuates the "anxiogenic-like" effect in the defensive burying paradigm but not in the elevated plus-maze following chronic cocaine in rats. *Psychopharmacology*, 145, 21-30.
- Harris, G. C., & Aston-Jones, G. (1993). Beta-adrenergic antagonists attenuate withdrawal anxiety in cocaine- and morphine-dependent rats. *Psychopharmacology*, 113, 131-136.
- Pinel, J.P.J., & Treit, P. (1978). Burying as a defensive response in rats. *J.Comp. & Physiol. Psychol.*, 92, 708-712.
- Sarnyai, Z., Biro, E., Gardi, J., Vecsernyes, M., Julesz, J., & Telegdy, G. (1995). Brain corticotropin-releasing factor mediates 'anxiety-like' behavior induced by cocaine withdrawal in rats. *Brain Res.*, 675, 89-97.
- Treit, D., Pinel, J. P., & Fibiger, H. C. (1981). Conditioned defensive burying: a new paradigm for the study of anxiolytic agents. *Pharmacol., Biochem., Behav.*, 15, 619-626.

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