Does Methamphetamine (MA) Cause Cognitive and Neurological Deficits? An Ecologically Valid Approach

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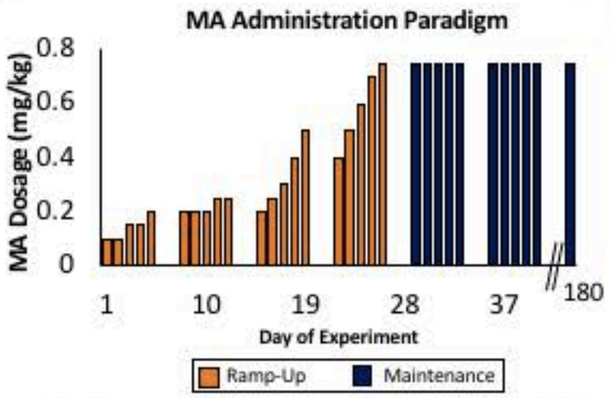
Methamphetamine (MA) Use Disorder is a growing public health concern in the United States. MA is widely believed to cause cognitive and neurological deficits. However, current **animal constructs of MA abuse do not model human use patterns.** MA users start at a low dose and ramp-up to ~0.75 mg/kg. Current models employ higher MA doses (~3-15 mg/kg), often lack a ramp-up period, and are rarely longitudinal. **This proposal will investigate whether an ecologically valid model of MA abuse will demonstrate poor cognitive and neurological outcomes** seen in current models.

Design



- 48 mice completed a cognitive pre-test (n=12 per task) prior to MA administration
- MA was administered via injection to n=40 mice 2x/day, 5 days/week, for 180 days
- Days 1-30 = "ramp-up" period
- Days 31-180 = "maintenance" period
- Mice completed cognitive post-test on day 184 and were sacrificed for immediate early gene (IEG) analysis
- * = expected $p \leq 0.05$; ** = expected $p \leq 0.01$ for t-tests performed

Conclusions

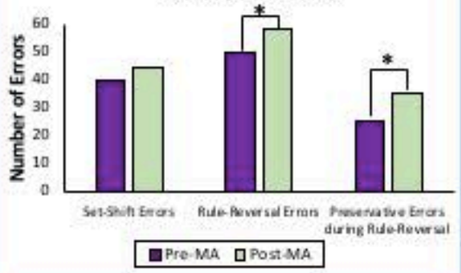
- This study will clarify whether MA abuse causes cognitive and neurological deficits
- We predict that MA will cause **minor yet statistically significant deficits** in IEG expression in **caudate nucleus** and **nucleus accumbens, delay-discounting,** and **perseverance errors** in cognitive flexibility
- These findings will inform MA Use Disorder treatments, as some clinicians feel that patients must be too cognitively impaired to respond to cognitive-behavioral treatments

Cognition

Cognitive Flexibility

Set-Shift/Rule-Reversal Task (SSRR)

Expected Set-Shift/Rule-Reversal Task Performance

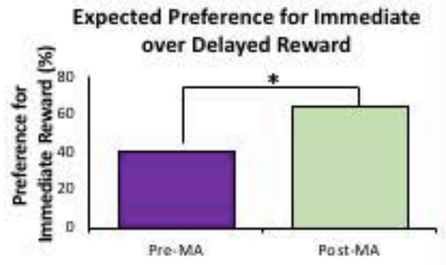


Decision-Making

Delay Discounting Task (DD)

- Tested for 7 days, with delay increasing each day
- Delays studied: 1, 10, 20, 40, 60, 80, & 100 seconds

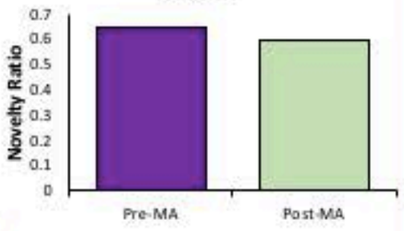
Expected Preference for Immediate over Delayed Reward



Long-Term Memory

Novel Object Recognition Task (NOR)

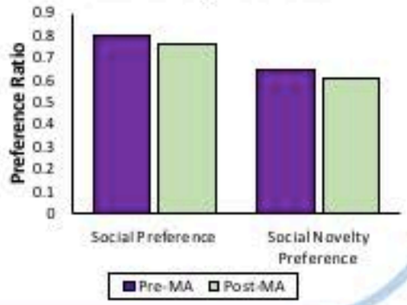
Expected Preference for Novel Object



Social Cognition

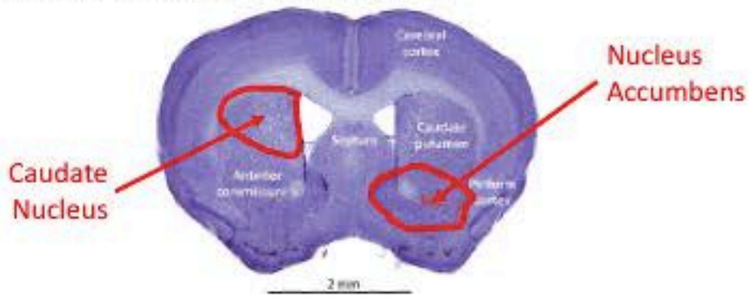
Social Preference Social Novelty Task (SPSN)

Expected Social Preference/ Social Novelty Preference

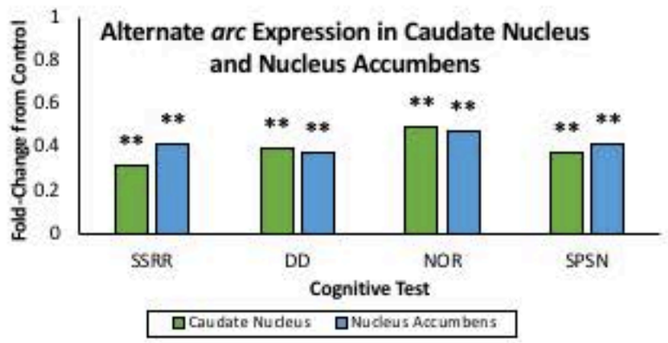


Neural Histology

Caudate Nucleus: memory, reward, motivation, and learning
Nucleus Accumbens: motivation, reward, operant conditioning
Immediate Early Gene: *arc.* Proxy for neuronal activity. Measured via brain dissection and qPCR.



Alternate *arc* Expression in Caudate Nucleus and Nucleus Accumbens



Expected *arc* Expression in Caudate Nucleus and Nucleus Accumbens