REPURPOSING NOREPINEPHRINE ANTAGONISTS FOR DRUG ADDICTION TREATMENT: A NOVEL TRANSLATIONAL LABORATORY BIOMARKER APPROACH FOR PHASE 2A CLINICAL TRIALS

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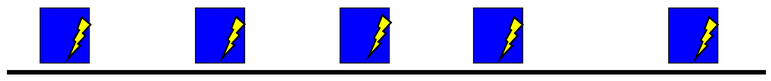
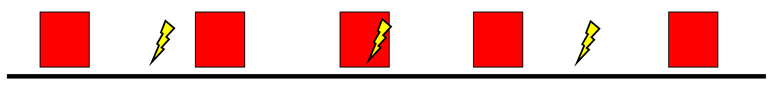
Background & Significance

- Stressors contribute strongly to drug use and relapse among both human drug dependent users and in rodent models of addiction.
- Norepinephrine (NE) and corticotropin-releasing factor (CRF) mediate behavioral responses to both acute stressors and drug deprivation.
- Uncertain (vs. certain) stressors in particular elevate brain NE/CRF levels and trigger reinstatement of drug-seeking behavior in rodents.
- NE and CRF antagonists reduce the stress response to uncertain stressors and block stress-induced reinstatement of previously extinguished drug-seeking behavior in rodents.
- Our laboratory has helped to validate a human model of stressor reactivity that has:
  - Strong method and measure ties to preclinical literature in rodents & non-human primates.
  - Shown reliable, robust effects of drug administration & drug deprivation in dependent users.
- This stress-reactivity paradigm may be utilized as a surrogate endpoint in Phase 2a RCTs.

Predictable Shock Block (Certain Threat)



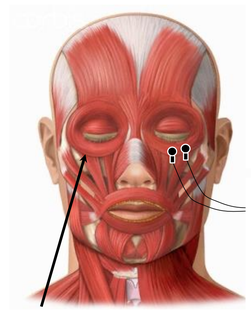
Unpredictable Shock Block (Uncertain Threat)



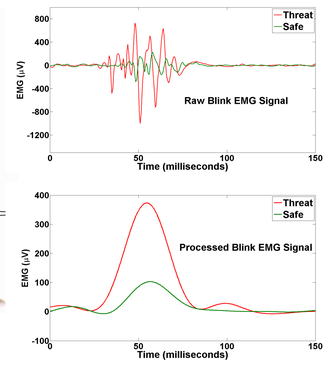
= Electric Shock to Fingers

Stress-Reactivity Task & Startle Response Measurement

- Participants view blocks of a series of 5 second colored square cues.
- Two within-subject cue conditions:
  - **Predictable shock:** shock during cues only.
  - **Unpredictable shock:** shocks at any time.
- The startle response is an adaptive defensive reflex that is preserved across species including rodents, non-human primates and humans.
- The startle reflex increases when the organism is threatened.
- Measure eyeblink response to brief bursts of white noise in humans.
- Startle potentiation = Threat cues - No-Shock cues (not displayed)

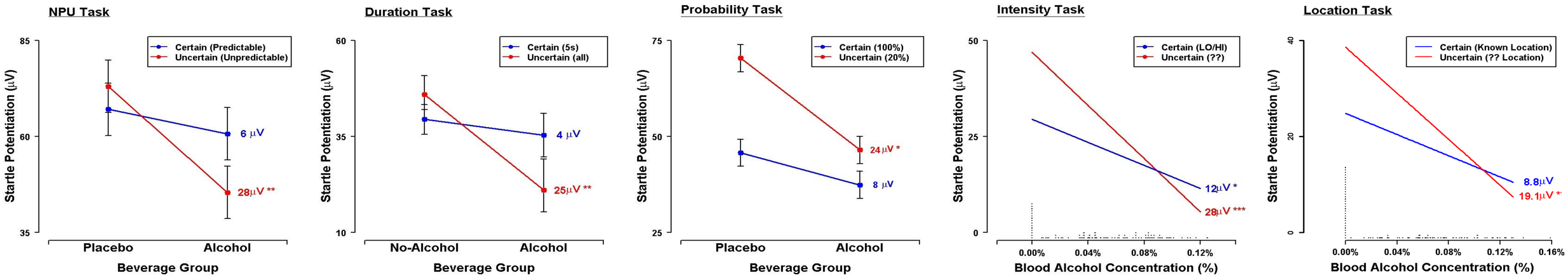


Orbicularis Oculi



Stress-Response Dampening Effects: Alcohol Administration Studies In Social Drinkers

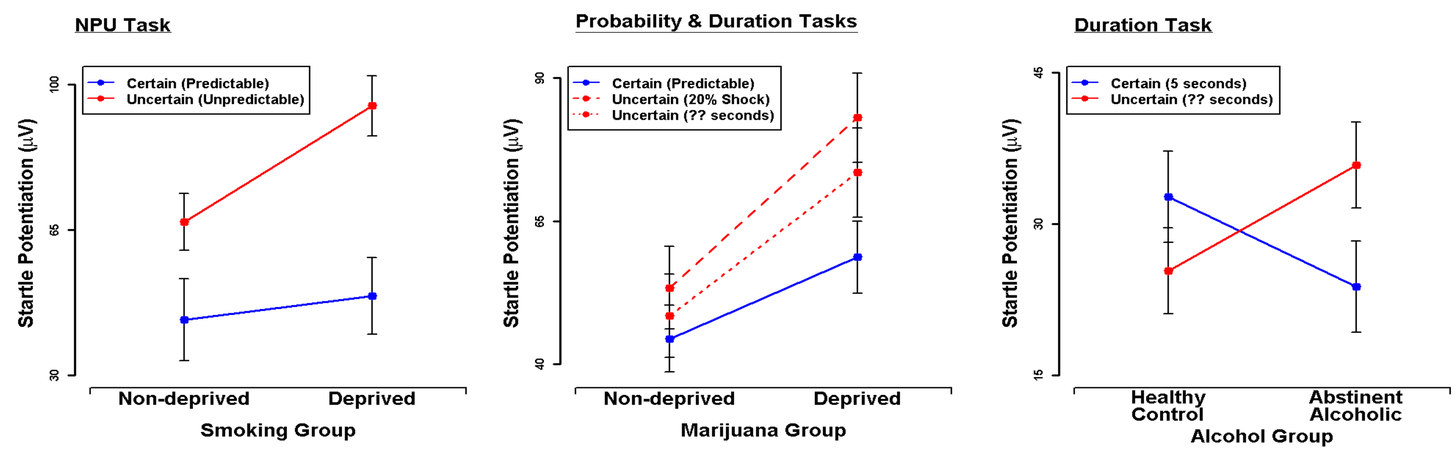
- Alcohol administered in two beverage groups (3 experiments):
- Control Group (No-alcohol or Placebo) vs. Alcohol group (target BAC = 0.08%)
- **Participants:** "Social" drinkers with no significant problems with alcohol use.
- Alcohol dose response (2 experiments): BAC range: 0.00% - 0.16%



- **Results:** Alcohol intoxication reduces stress-reactivity, measured via startle potentiation, especially during uncertain relative to certain threat. This finding is consistently observed across five conceptual replications that manipulate uncertainty regarding only one characteristic about the stressor/threat at a time: When, If, How Bad, & Where.

Stress-Response Enhancing Effects: Drug Deprivation Studies In Tobacco, Marijuana Or Alcohol Dependent Users

- **Smoker Participants:** Regular heavy tobacco (Study 1) or marijuana (Study 2) users randomly assigned to one group:
  - Abstain from tobacco 24hrs or marijuana 3days
  - Continue normal ad libitum use prior to study
- **Drinker Participants:** Abstinent alcoholics 1-8 weeks since last drink and healthy controls (Study 3).
- **Results:** Drug deprivation increases stress-reactivity, especially during uncertain relative to certain threat.
- **Conclusions:** Biomarker of sensitized stress-reactivity in addicted individuals during periods of abstinence may reflect:
  - Risk marker for stress-induced relapse.
  - Surrogate endpoint to evaluate treatment efficacy.



Phase 2a Clinical Trial: Screening Prazosin As Treatment Of Stress-Induced Relapse In Alcoholism

Objectives & Aims

- **Objective 1:** To confirm norepinephrine alpha1 receptor involvement in startle potentiation during unpredictable stressors in humans with alcoholism.
- **Objective 2:** Evaluate efficacy of initial (2mg) and therapeutic (15mg) dose of Prazosin at reducing stressor-reactivity among alcoholics in early abstinence and the relationship of this biomarker to treatment/relapse outcomes.
- **Aim 1:** Examine the effects of initial dose Prazosin (2mg vs. placebo) on responses to unpredictable stressors in abstinent alcoholics.
- **Aim 2:** Examine effects of a therapeutic dose Prazosin (15mg vs. placebo) on responses to unpredictable stressors.
- **Aim 3:** Examine predictive validity of laboratory biomarkers of stress-reactivity on 2-week relapse outcomes.

Method

- **Design:** Double-blind, placebo-controlled, mixed design, cross-over study.
- **Participants:** Abstinent alcoholics 1-8 weeks since last drink.
- **Drug:** Prazosin is a brain-penetrant norepinephrine alpha1 receptor antagonist.
- **Initial Dose:** Administer 2mg Prazosin and Placebo on two separate laboratory visits 2-7 days apart (order randomized & counterbalanced within-subjects).
- **Therapeutic Dose:** Participants titrate to 15mg Prazosin or Placebo (randomized between-subjects) over 2 weeks following 2nd initial laboratory visit.
- **Stress-Reactivity Task:** Assessed at 2 initial study visits (Aim 1: 2mg vs. Placebo; within-subs) and 3rd study visit following 2 week titration (Aim 2: 15mg vs. Placebo; between-subs).
- **Treatment Outcome:** Relapse to alcohol use is assessed after two weeks of Prazosin (Aim 3).

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