

**Administrative Core - INIA: Stress, Anxiety and Alcohol Abuse**  
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**A. LEAD APPLICATION: ADMINISTRATIVE CORE**

We plan to extend the cross species approach that we have used previously to explore and test neural mechanisms that link stress, anxiety, and excessive alcohol intake. We have further refined our INIAstress projects and cores to inform us about the interaction of stress and ethanol. This has been done in part by exploiting a restricted set of standard operating procedures to induce stress, evaluate anxiety, expose subjects to ethanol, and measure responses to ethanol. Within this framework we have designed experiments to discover and characterize the complex interactions of genetic and non-genetic factors that contribute to stress-associated risk for excessive drinking. Collectively, these collaborative studies will allow us to more directly integrate data from behaviors to brain mechanisms to genes within a scope of expertise and thematic inquiry that would be difficult to attain using more traditional grant mechanisms (R01s or P50).

The specific aims of the Administrative Core are to:

1. Provide scientific leadership on the consortium's theme of stress, anxiety and alcoholism
2. Provide the administrative center for the INIA Consortium for the overall management, direction and coordination of the consortium. This includes insuring oversight by the Scientific Advisory Panel and the INIA Steering Committee, as well as coordinating the interactions of the different research and core components of the INIA.
3. Oversee and evaluate the Pilot Projects Component of INIA
4. Promote the inclusion of neuroscientists in the area of stress and anxiety who are new to the alcohol field as well as alcohol investigators that are interested in studying the interaction of stress and anxiety on mechanisms of alcohol.

The goal of this INIA consortium is to organize our integrated efforts and define genetic and environmental influences on the brain mechanisms that mediate responses to alcohol, the response to stress and the reciprocal relationship between excessive drinking, the physiological state of stress, and the subjective state of anxiety. Through this characterization we will help to define an individual's risk for the development of alcoholism and make progress towards discovering novel, effective, and tailored interventions and treatments.

Our overall INIAstress hypotheses are:

1. Gene variants contribute to highly variable risk of excessive alcohol intake and also modulate differential responses to stress, and alcohol's effects on these responses
2. Alcohol directly interacts with neural circuitry involved in stress responses. We hypothesize that the actions of alcohol in amygdala, the bed nucleus of the stria terminalis (BNST), hippocampus, nucleus accumbens, and prefrontal cortex alter key synaptic function to reduce anxiety-related responses and reinforce excessive alcohol intake. We also hypothesize that effects of ethanol on the function of neurotransmitter receptors and transporters, neurotransmitter release, and channel function contributes to this anxiolytic action.

3. Neural circuitry involved in stress responses are also involved in mediating the reinforcing effects of ethanol. Neurosteroids are a common link in these circuits. We hypothesize that ethanol and stress interact at the level of brain circuitry, and that perturbations in one system can determine outcome of the other system and synergistically produce dysfunctional outcomes.
4. Excessive and prolonged exposure to alcohol gives rise to new steady-state levels of HPA activity which are revealed under acute stress or abstinence and can promote further, excessive intakes of ethanol.