VTA Neuron Dopaminergic Circuitry Change Following Chronic alcohol Exposure

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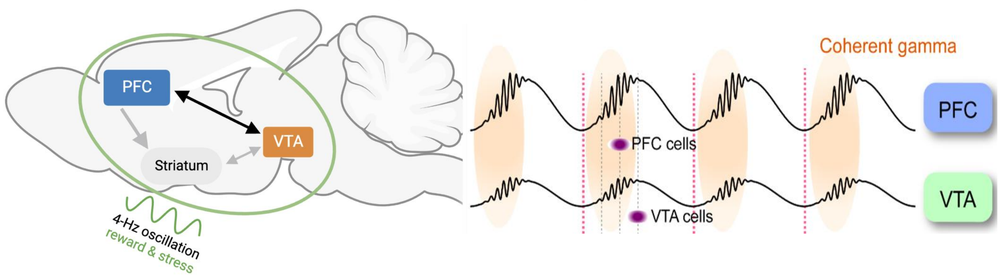
Introduction

The Ventral Tegmental Area (VTA), best recognized as the hub of mesocorticolimbic circuitry processing emotion, motivation, and reward, contains both dopaminergic neurons (65%) and GABAergic interneurons (35%). In addition to local inhibition of VTA dopaminergic neurons, Ventral Tegmental Area (VTA) GABA neuron also exerts inhibition to distal brain regions.[1] The diverse functions of VTA GABA neurons render them effective reward and aversion mediators. Since alcohol and stress are powerful modulators of VTA GABA neurons, our goal for this research is to investigate the role that VTA GABAergic neurons play in physiological and behavioral responses to alcohol. We use the stimulant response to alcohol as an index of its impact on this mesocorticolimbic circuit.

Interestingly, recent research revealed that inattentive stressful and rewarding experiences activate contiguous neuronal populations in the Prefrontal Cortex (PFC) and the VTA. This prompt our second interest of investigating how withdrawal from alcohol affects the dopaminergic mesocortical circuit by looking at connectivity between VTA and PFC.



- **Is stimulant effect of acute alcohol associated with induction of a 4Hz "reward" signal in the VTA?**
- **Does repeated alcohol (in a manner that induces sensitization) alter this 4Hz "reward" response to alcohol OR to natural reward (cookie)?**

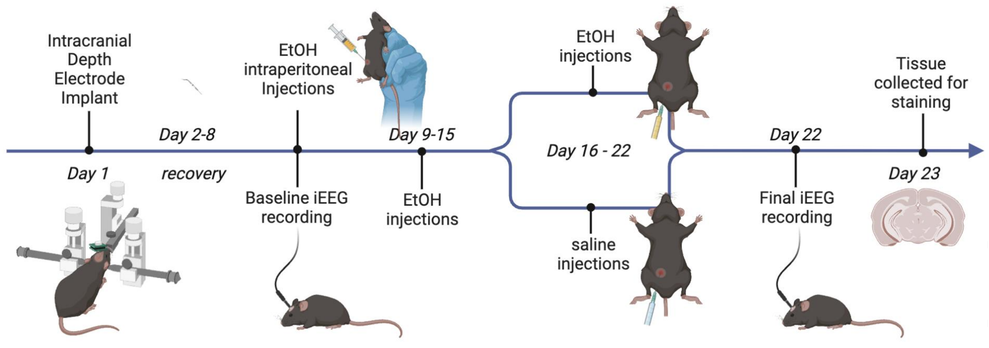
Methods

Sample

- 11 C57BL/6J male mice

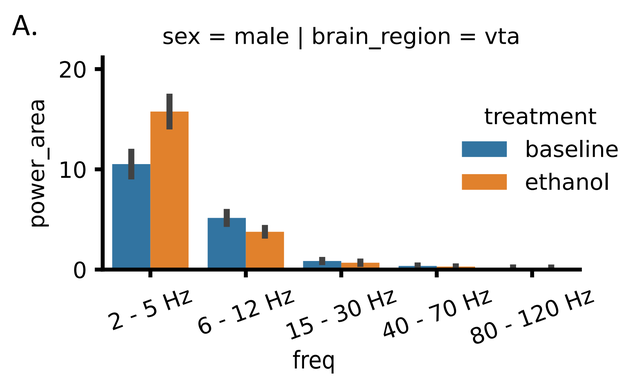
Measures

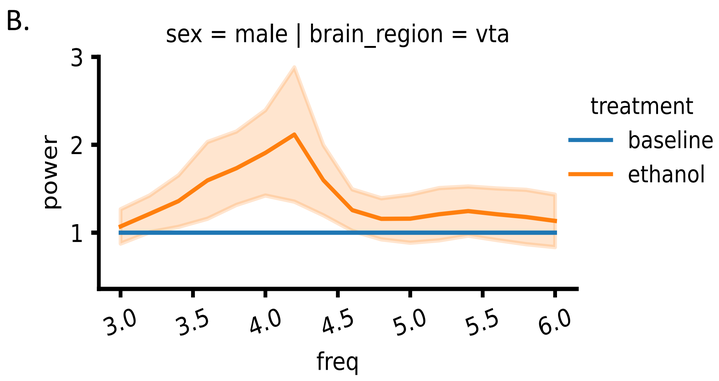
- One week prior to behavioral testing and recording, mice were implanted with head mounts containing a depth electrode targeting the VTA, a stainless-steel screw targeting the prefrontal cortex (For EEG), and ground & reference screws.
- On the first day of data collection, the male mice were placed in an open field arena tethered to a recording apparatus. The local field potential (LFP) data and behavior were recorded at baseline for 10 minutes and after acute alcohol(alcohol; 2.0g/kg) exposure via intraperitoneal injection (IP) for 20 minutes. For the following 2 weeks, 6 mice were administered alcohol (20% v/v) at 2g/kg once a day via IP injection. 5 mice received saline injections after the first week of alcohol injections for a withdrawal effect.
- After 2 weeks, the same data collection procedure was followed with the addition of a cookie exposure during the last 5 min of behavior.
- Acquired LFP data was analyzed using custom python scripts to break down the signal into component parts using the fast fourier transformation.



Results

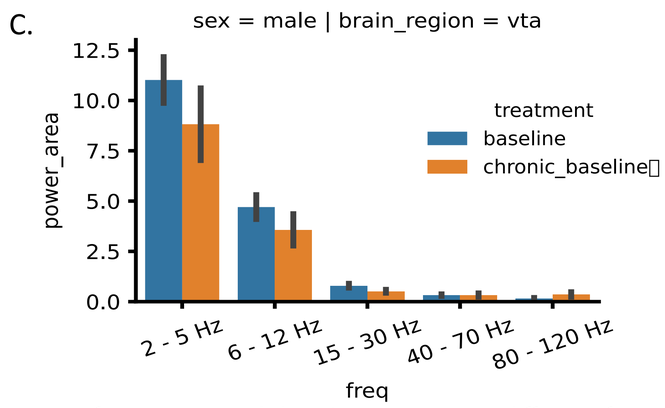
1. Acute alcohol exposure induces a 4 Hz "reward" signal in VTA in male mice.

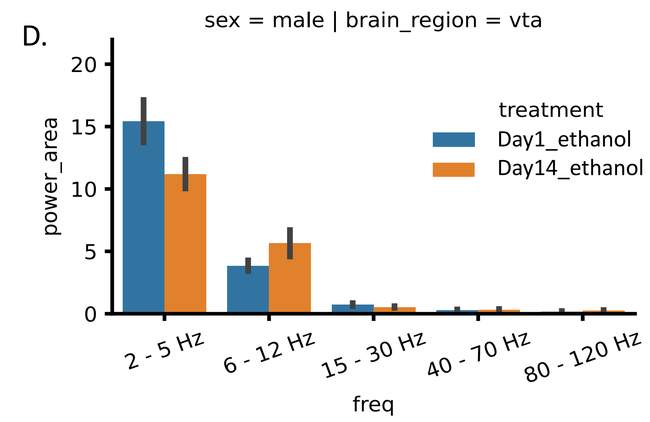




A: power-frequency graph comparing different frequency bands, in which the 2-5 Hz band is showing the greatest difference between baseline and alcohol B: detailed baseline normalized power-frequency graph selecting 3-6 Hz, suggesting an upregulation in the 4Hz reward oscillation in the VTA (shown as comparison with baseline).

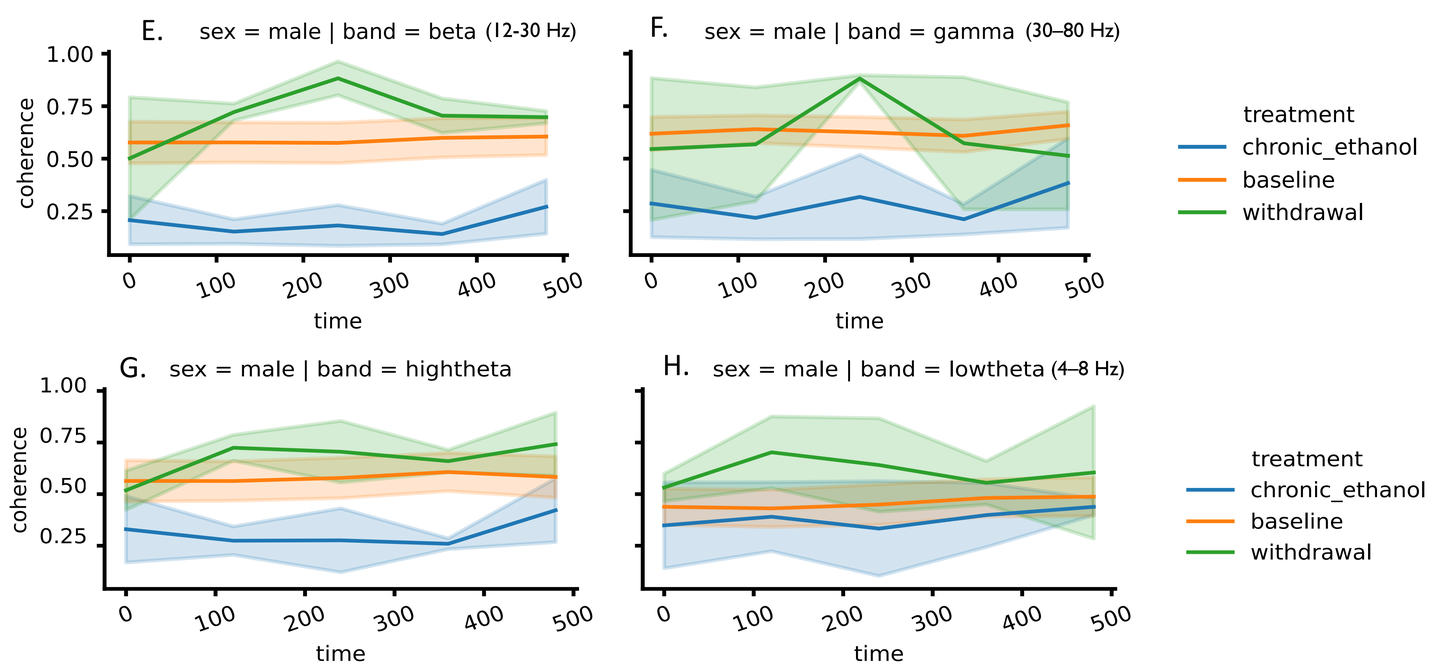
2. Chronic (2 weeks of daily) alcohol exposure dampens reward signal





C&D: power-frequency graph baseline comparing different frequency bands, baseline measure following chronic ethanol exposure (Day 14) displays less expression on 2-5 Hz band compared baseline before alcohol exposure (Day 1). Chronic alcohol (Day 15) shows less rewarding signal as compared to signaling following just acute ethanol exposure (Day 1).

3. Chronic alcohol exposure results in less connectivity between VTA and PFC, while withdrawal results in more connectivity at lower bands.



E&F&G&H: coherence of activity between VTA and PFC across time at different oscillation bands. Withdrawal from alcohol after a week of exposure induces increase (~0.75) in the phase coherence between VTA and PFC as compared to baseline (~0.6), while chronic exposure to alcohol has the opposite effect (~0.35).

Discussion

- Brain oscillations are produced by the fluctuating interactions between inhibitory (GABAergic) interneurons and Dopaminergic cells.[3]
- Among these various oscillation frequencies, 4Hz predicts the degree of subsequent reward-seeking. Previous research has demonstrated the mediating function of VTA GABAergic neurons in stress-induced reward seeking[4]. Inhibiting VTA GABAergic neurons disrupted stress-induced oscillations and reduced reward-seeking behavior.
- When stress becomes chronic, the VTA dopaminergic circuit becomes less active, which may result in degeneration and microglial activation.[5] The less coherence between VTA and PFC in result 3 supports this conclusion.
- In the future, we plan to include female mice in the study and investigate gender differences in the mechanisms generating sensitization to alcohol-induced locomotion and the adaptations in the mesocorticolimbic signaling after alcohol exposure.

REFERENCES

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