Acute Ethanol Effects on Global Brain Activity and Functional Connectivity: A BOLD MRI Study in Awake Rats

Athreya, D.S.*, Axe, B.*, Cavallaro, N., Moore, A., Kulkarni, P.P, Ph.D., Ferris, C.F. Ph.D.

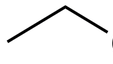
Northeastern University

Northeastern University
Center for Translational Neuro-imaging

* delineates co-first authorship

Background

Alcohol is one of the most widely consumed psychoactive substances, impacting cognitive and behavioral processes through complex interactions with neural circuitry. Its acute effects on brain function vary depending on dosage, leading to distinct activation and inhibition patterns within specific brain regions and networks. Given its widespread use and addictive potential, understanding these neural dynamics is critical. Pharmacological functional MRI (phMRI) provides a powerful technique to capture real-time changes in brain activity. By investigating these patterns, research can clarify how alcohol alters normal neural processing and contributes to both acute intoxication and potential long-term neural adaptations.



Methods

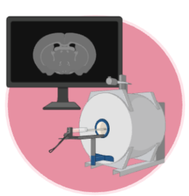
Alcohol Exposure

- Sprague-Dawley Rats (N=12 Sex Split)
- Within-subjects Lattice Randomization of Subjects
- 16% Ethanol in Saline W/V
- Intraperitoneal catheter injections
- Three experimental groups (1, 2, and 3 g/kg) and one vehicle control group



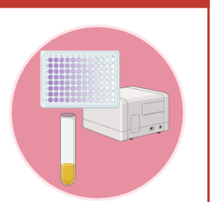
Neuroimaging

- 70/20 7T Bruker MRI
- BOLD fMRI
  - 5 minute baseline
  - 20 minute stimulus time
- Resting-state Functional Connectivity (rsFC)
- Within-subjects Latin square design utilized for each rat over four scans to randomize dose orders for a total of 48 scans (12 per-dose).



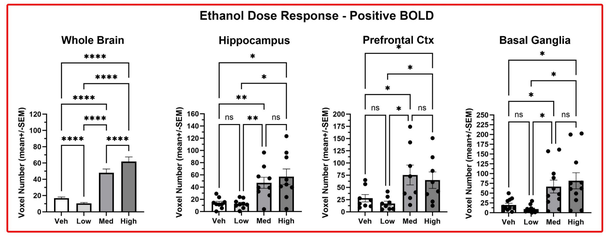
Blood Alcohol Level Measurements

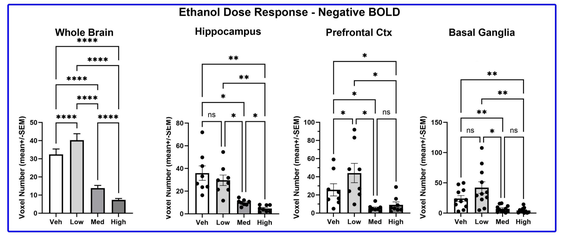
- Spectrophotometry Assay
- Tail blood collected 30 minutes post-injection,
- Standard-curve generated according to the manufacturer's protocol for quantitative BAC analysis.
- BAC-BOLD-rsFC Correlations

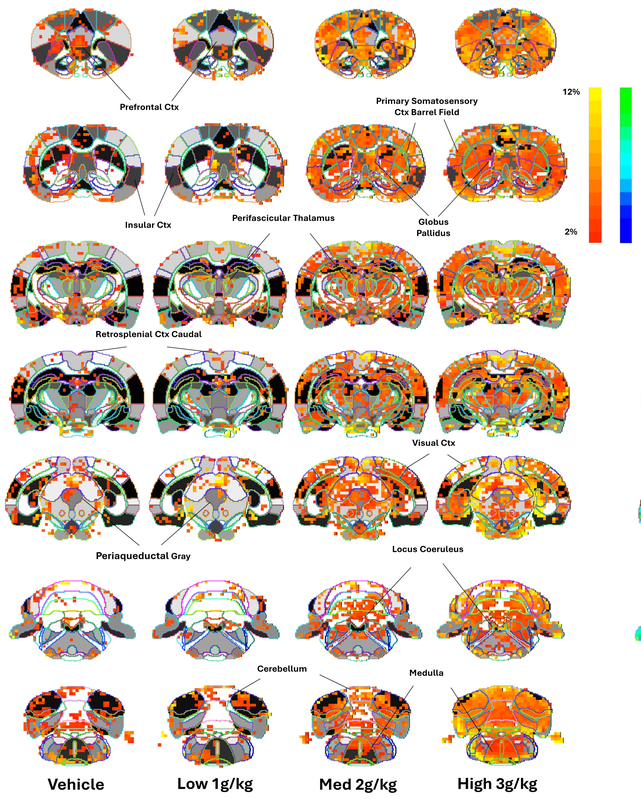


Pharmacological fMRI and Functional Connectivity

Pharmacological fMRI – Positive and Negative BOLD Changes







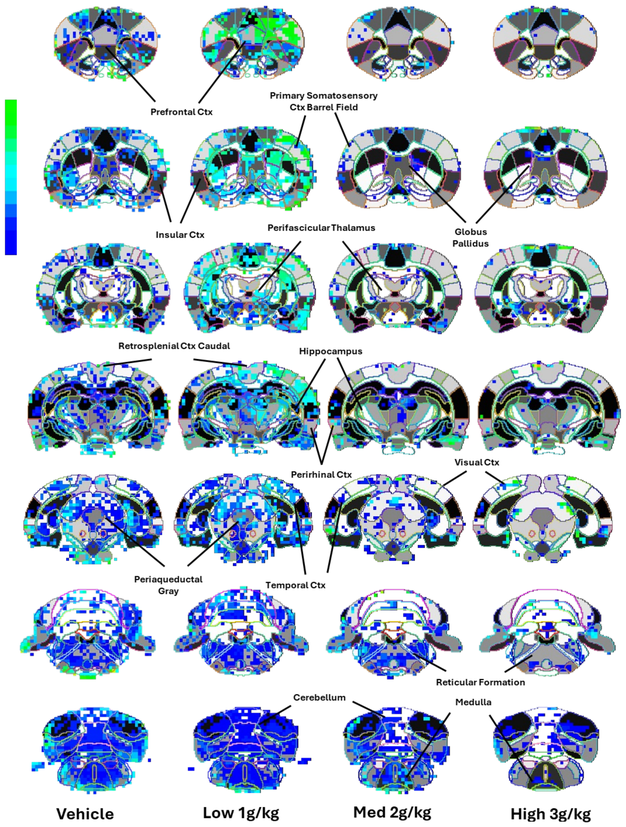
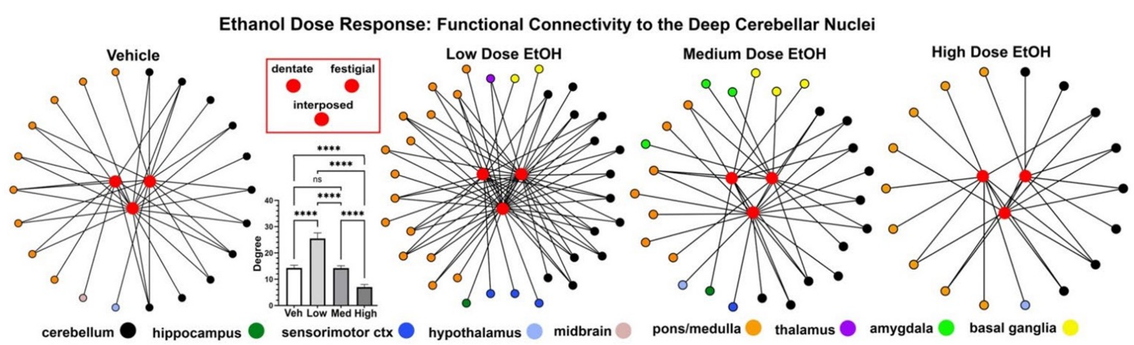


Figure 4 Connectivity to Cerebellar Nuclei



Discussion

- Ethanol exposure induced complex, dose-dependent neural activity changes, challenging traditional views of uniform neural suppression at high doses.
- Blood alcohol concentrations measured 30- minutes post-injection confirmed dose-proportional increases across treatment groups.
- **Lower ethanol doses** decreased positive BOLD signaling and increased negative BOLD signaling.
- **Higher ethanol doses** unexpectedly resulted in increased positive BOLD signals and decreased negative BOLD responses, potentially due to ethanol's known vasodilatory properties enhancing cerebral blood flow.
- **Resting-state functional connectivity (rsFC)** showed a U-shaped dose-dependent alteration, highlighting ethanol's impact on global and region-specific brain connectivity.
- Specific brain regions including the thalamus, hippocampus, piriform cortex, sensory cortex, and cerebellum displayed distinctive connectivity responses, suggesting differential sensitivity to ethanol's effects.
- Dose-dependent changes in cerebellar connectivity were observed, with the greatest expansion of cerebellar-extracerebellar coupling at the low dose, suggesting even modest ethanol exposure can substantially reorganize cerebellar networks.
- Prefrontal network connectivity expanded at the low dose, but contracted back to baseline at the medium and high doses.

Future Directions

- Future studies integrating serial BAC measurements could provide a more comprehensive understanding of the temporal aspects of ethanol's neuromodulatory effects.

Acknowledgments

EKAM
THE IMAGE OF DRUG DISCOVERY

NIH National Institute on Drug Abuse