Chronic binge alcohol induces hippocampal and cingulate plasticity in SIV-infected female rhesus macaques

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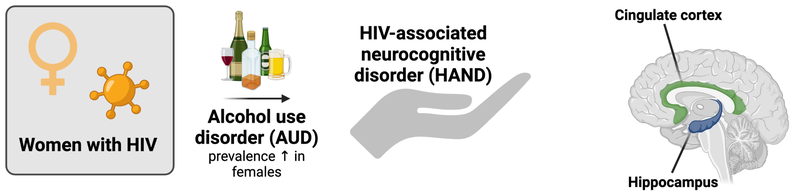
LSU Health NEW ORLEANS School of Medicine

NIH National Institute on Alcohol Abuse and Alcoholism

Background



- Chronic HIV infection → **HIV-associated neurocognitive disorder** (**HAND**), a leading comorbidity of HIV
- Cognitive deficits associated with HAND are further exacerbated by **chronic alcohol use,** and there's a rising prevalence of alcohol use disorder (AUD) in **women.**
- The **cingulate cortex** and **hippocampus** are two brain regions involved in cognition that may be affected in HAND.

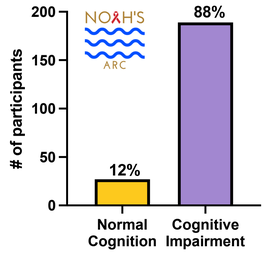


Figure 1: Data from the New Orleans Alcohol Use in HIV (NOAH) study found a high prevalence of cognitive impairment among the NOAH participants as assessed by the Montreal Cognitive Assessment (MoCA) with 88% of the cohort receiving a score indicating some level of cognitive impairment.

Hypothesis:

SIV-infected, ART-treated female rhesus macaques with a history of CBA administration will exhibit increased excitability of brain areas involved in cognition, including the hippocampus and cingulate cortex.

Methods

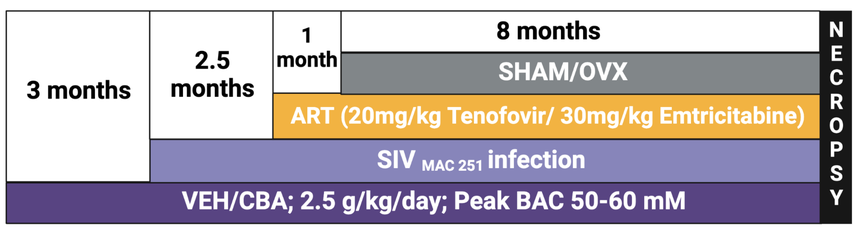
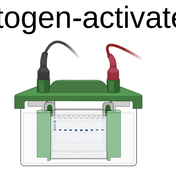


Figure 2: Experimental timeline for macaque study. Adult female rhesus macaques (n=7-8 per group) received CBA or VEH for a total of 14.5 months, were intravaginally inoculated with SIV for 11.5 months, and treated with ART for 9 months. Ovariectomy (OVX) or sham surgery was performed at 6.5 months.

- **Four experimental groups**
  - VEH/SHAM, CBA/SHAM, VEH/OVX, CBA/OVX
- **Western blotting**
  - At necropsy, brains were snap-frozen and regional brain dissections were taken from 6mm coronal brain slices and guided by the Paxinos Rhesus Macaque Brain Atlas.
  - Regions analyzed include the cingulate cortex (Brodmann area 24) and whole hippocampus.
  - Assessed phosphorylation and changes in total protein levels of proteins involved in glutamate and mitogen-activated protein kinase (MAPK) signaling pathways:
    - pGluR1^{ser845} and total GluR1
    - pNR1^{ser897} and total NR1
    - pERK and total ERK



CBA differentially alters hippocampal and cingulate glutamatergic and MAPK signaling

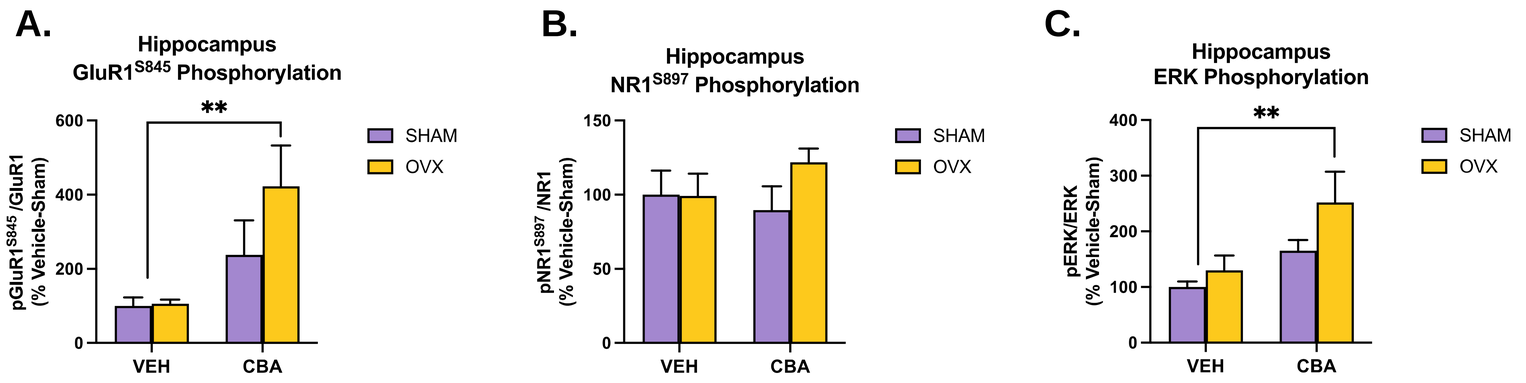


Figure 3: Chronic binge alcohol increases hippocampal phosphorylation of GluR1 (subunit of the glutamatergic AMPA receptor) (**A**, p=0.0054) and extracellular signal-regulated kinase (ERK; **C,** p=0.0093), but does not alter phosphorylation of NR1 (subunit of the glutamatergic NMDA receptor) (**B**). N=6 per group.

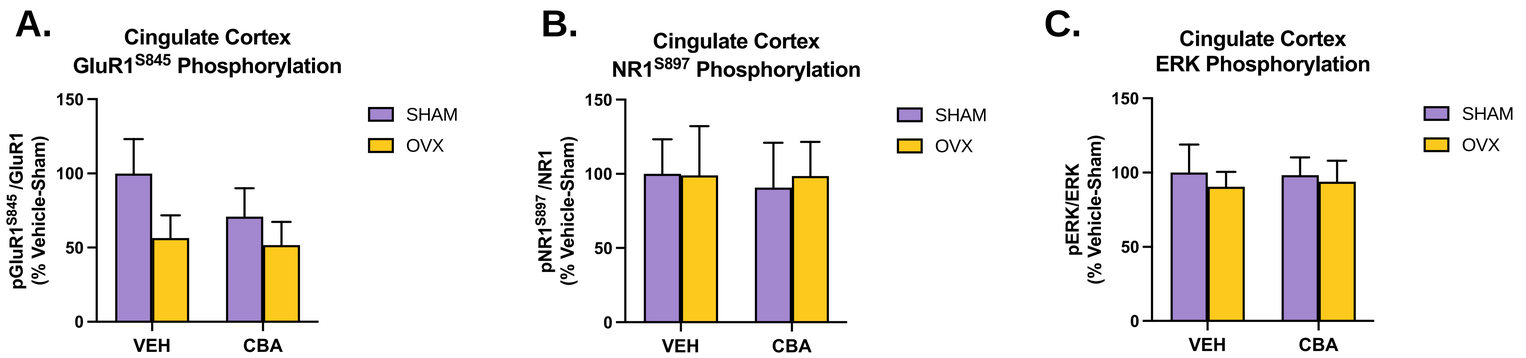


Figure 4: Chronic binge alcohol does not alter phosphorylation of GluR1 (**A**), NR1 (**B**), or ERK (**C**) in the cingulate cortex. N=6 per group.

Conclusions and Future Directions

- Our data indicate that there are regional excitability differences in the brain produced by chronic binge alcohol (CBA) exposure, with differential effects of CBA on GluR1 (AMPA receptor subunit) in the hippocampus and cingulate cortex.
- CBA also increases hippocampal mitogen-activated protein kinase (MAPK) signaling through increased phosphorylation of ERK.

These findings will inform future human and non-human primate studies examining specific cognitive domains associated with these regions.

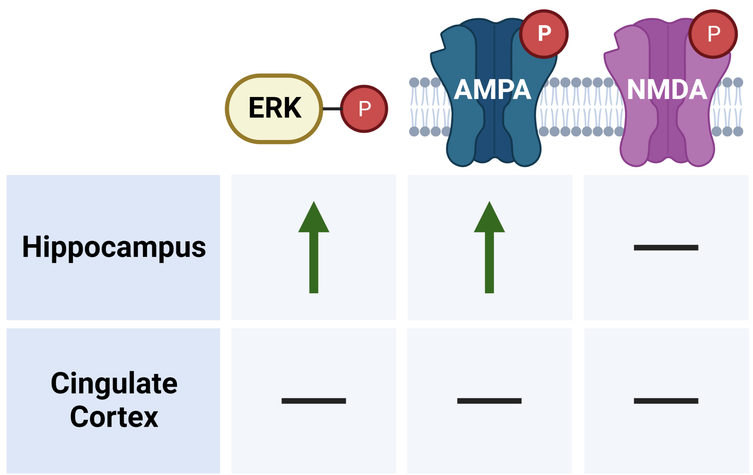


Figure 5: Chronic binge alcohol increases phosphorylation of AMPA and ERK but does not alter phosphorylation of NMDA in the hippocampus. Chronic binge alcohol does not alter phosphorylation of ERK, AMPA, or NMDA in the cingulate cortex.

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