Neurobiological consequences of chronic binge alcohol exposure and ovariectomy on markers of hippocampal plasticity in SIV-infected female rhesus macaques

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Introduction

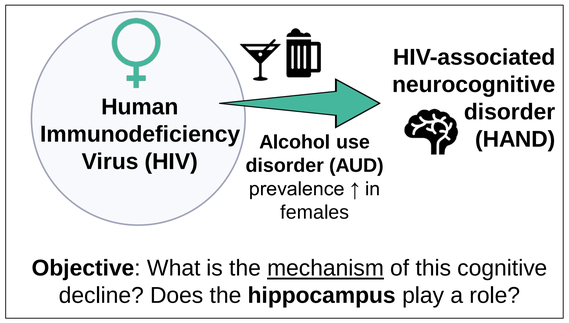


Figure 1: Excessive alcohol consumption by women living with HIV may exacerbate cognitive decline and progression to HIV-associated neurocognitive disorder (HAND).

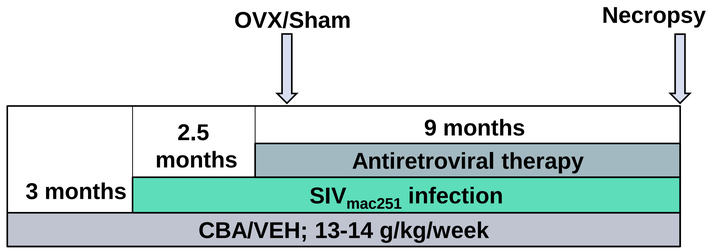
Objective: What is the mechanism of this cognitive decline? Does the **hippocampus** play a role?

- **3 implicated neuroendocrine signaling pathways:**

Glucocorticoids	• Stress hormone, ↑ as a result of chronic alcohol use and withdrawal
Estrogen	• Sex hormone, neuroprotective, may ↓ during chronic alcohol use
Brain-derived neurotrophic factor (BDNF)	• Growth factor, role in neuronal health, may ↓ during chronic alcohol use

- **Hypothesis**: We predict simian immunodeficiency virus (SIV) infected, ART-treated female rhesus macaques with a history of chronic binge alcohol administration (CBA) and ovariectomy (OVX) will demonstrate decreases in hippocampal BDNF and estrogen signaling, along with increases in glucocorticoid signaling (n=7-8 per group). We further predict novel object recognition task data will reveal cognitive deficits in the CBA and OVX groups.

Experimental Timeline



- **Novel object recognition (NOR) tasks** were conducted the week before necropsy for each animal and included a familiarization phase (trial 1), when animals were presented with two of the same object, and a testing phase (trial 2), when animals were presented with the same object from trial 1 and a novel object.

Methods

- **NOR tasks** were scored for the latency to approach both objects and the time spent investigating each object for trials 1 and 2.
- Brains were snap frozen at necropsy, and the hippocampus was homogenized for protein extraction and analysis.
- **Western blotting** was used to assess phosphorylation of proteins and changes in total protein levels in three signaling pathways (GR, ER, and BDNF).

Pathway	Hippocampal Proteins
GR	**pGR$^{S211/232}$**, pGR^{S226},11βHSD-1
ER	pER$^{S104/106}$, pER^{S118}, pER^{S167}, GPER
BDNF	BDNF, pTrkB, pPLCγ, **pERK**, pAkt

Table 1: A summary of signaling targets to be investigated in each pathway.

Novel Object Recognition Task Data

Trial 1

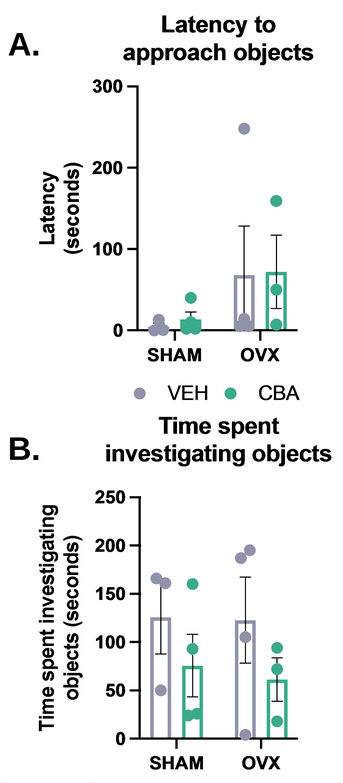


Figure 2: During the familiarization phase (trial 1), the OVX group showed a trend of increased latency, and the CBA group revealed a trend of decreased time spent investigating the objects.

Trial 2

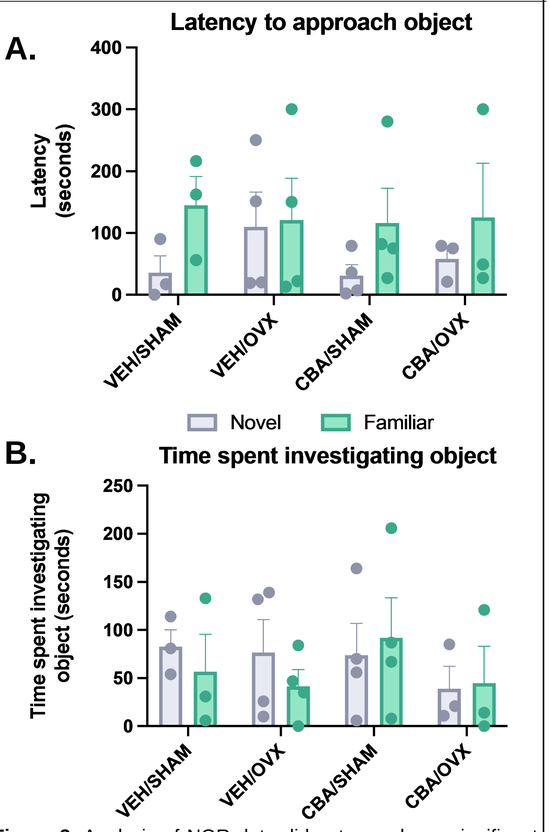


Figure 3: Analysis of NOR data did not reveal any significant changes in latency or time spent investigating the novel or familiar objects during the testing phase (trial 2).

Alterations in GR and ERK Phosphorylation

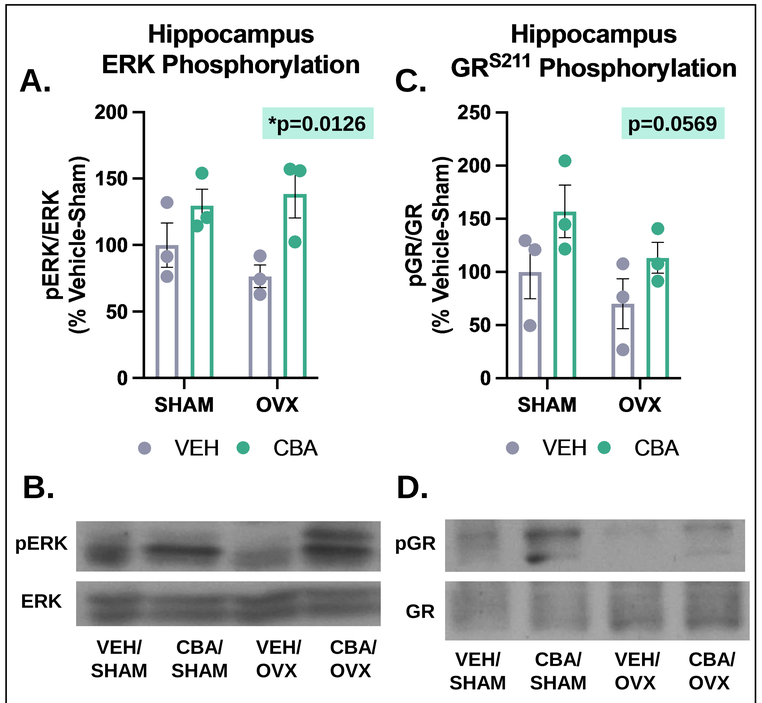


Figure 4: Western blot analysis revealed CBA administration significantly increased phosphorylation of extracellular signal-regulated kinase (**A.**, **B.**; p=0.0126) and resulted in a trend of increased phosphorylation of the glucocorticoid receptor (**C.**, **D.**; p=0.0569) and

Conclusions

- CBA administration and ovariectomy groups may alter NOR task performance in trial 1, potentially revealing **anhedonia**.
- CBA administration increases phosphorylation of ERK, a marker of neuronal plasticity, and results in a trend of increased GR phosphorylation, **indicating a potentiation of stress signaling.**
- Ovariectomy does not significantly alter phosphoprotein levels in any pathway.
- Future directions include completion of Western analyses, examination of additional proteins, and additional scoring of NOR experiments.

Our preliminary findings illustrate the therapeutic potential for reducing stress-related glucocorticoid signaling to combat hippocampal deficits produced by chronic alcohol use in women living with HIV.

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