



Addressing substance use disorders, HCV and neuropsychiatric impairments from a psychoneuroimmunology research perspective

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HIV/HCV/SUD Symposium

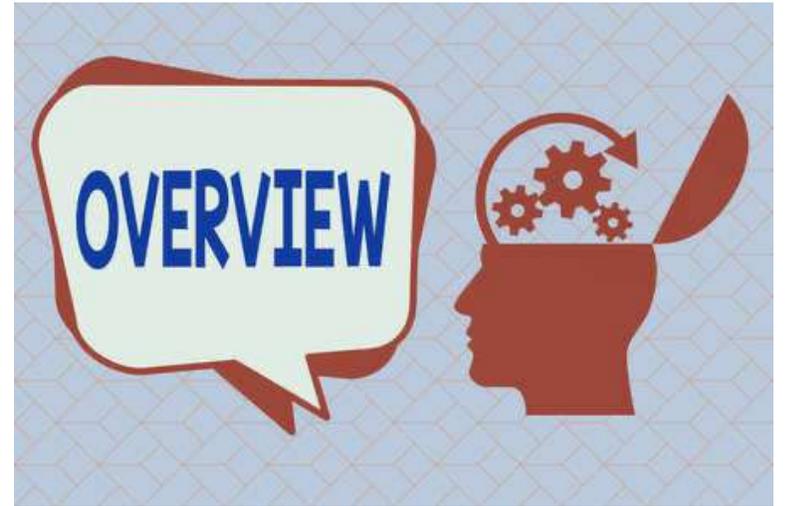
November 17, 2021

Disclosures

- The Department of Veterans Affairs (VA) and Oregon Health & Science University (OHSU) own the RTL technology used in the RTL research that is discussed in part of this presentation. The VA, OHSU, and Dr. Loftis have rights to royalties from the licensing agreement with Arielle Immunotherapeutics.
- These potential conflicts of interest have been reviewed and managed by the Conflict of Interest Committees at the VA Portland Health Care System and OHSU.

Presentation overview

- Background – substance use disorders, HCV, and inflammation
- Immune system targets for therapeutic development/intervention
- Immunomodulatory treatment strategies
- Future directions

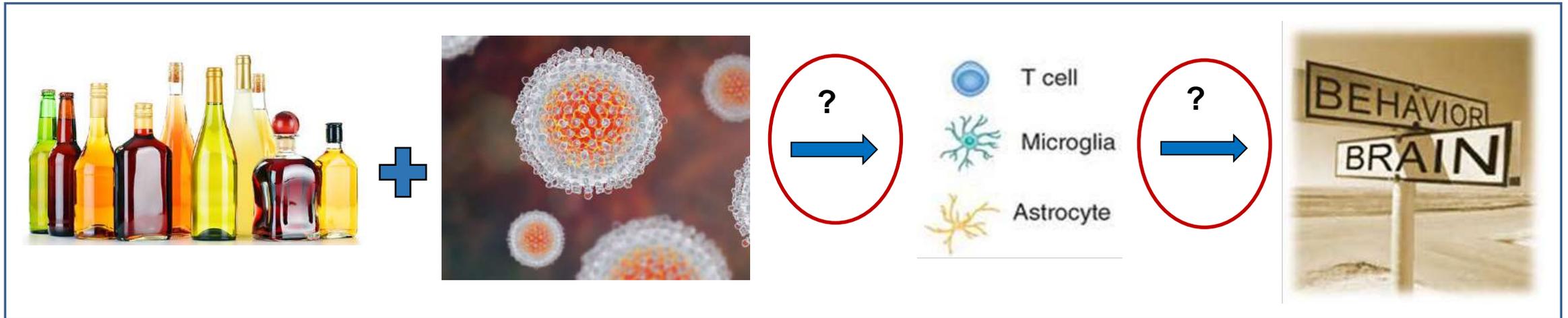
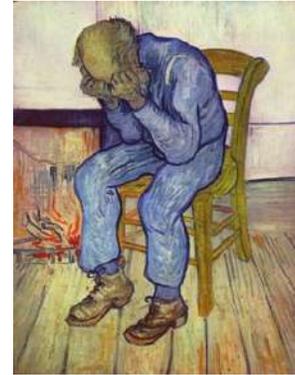


Learning objectives

1. Identify key inflammatory factors that contribute to psychiatric symptoms and cognitive impairments, particularly in the context of SUD and co-morbid viral infection
2. Describe current and emerging theories of SUD (alcohol and methamphetamine) and HCV effects on brain and neuropsychiatric function
3. Integrate the role of inflammatory mechanisms in the treatment of SUD, HCV and related neuropsychiatric impairments



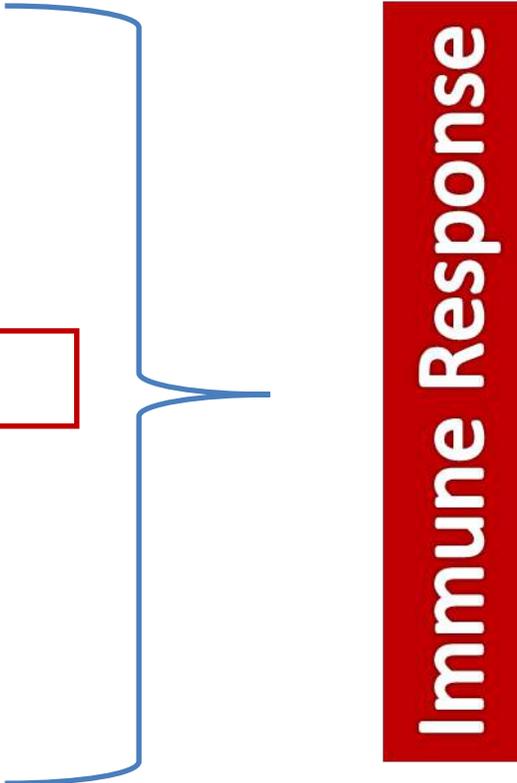
Translational psychoneuroimmunology



Why target the immune system for substance use disorders?

NIDA's Top 10 List

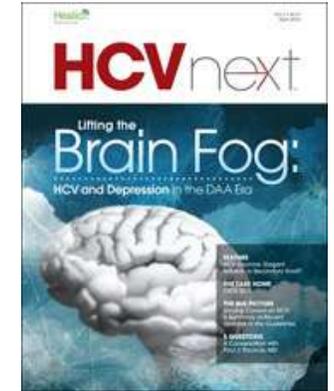
1. Nicotine
2. Alcohol
3. Opioids (*e.g.*, heroin)
4. Cannabinoids (*e.g.*, marijuana)
5. Stimulants (*e.g.*, cocaine, amphetamine, methamphetamine)
6. Club drugs (*e.g.*, MDMA, GBH)
7. Dissociative drugs (*e.g.*, ketamine, PCP and analogs)
8. Hallucinogens (*e.g.*, LSD, mescaline, psilocybin)
9. Other compounds (*e.g.*, anabolic steroids, inhalants)
10. Prescription medications (*e.g.*, opioid pain relievers)



Immune Response

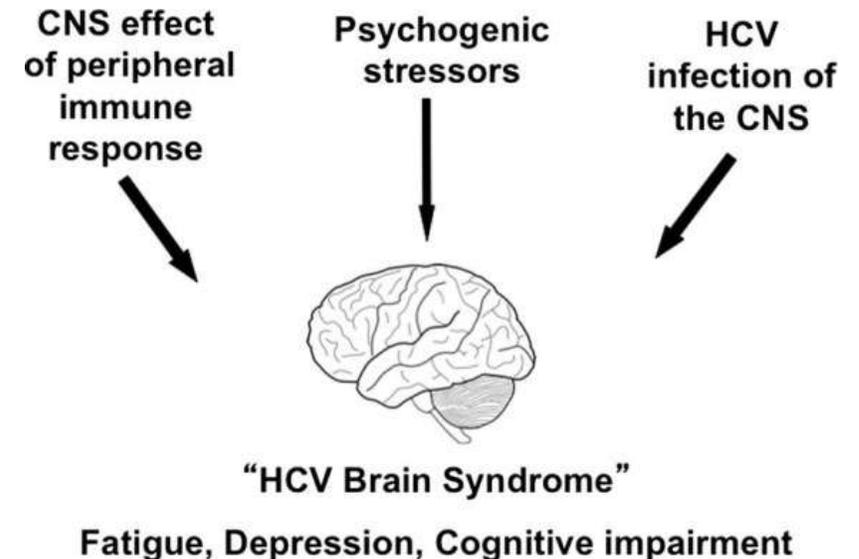
Chronic hepatitis C virus (HCV) is associated with a variety of extrahepatic effects

- central nervous system (CNS) damage
- neuropsychiatric impairments

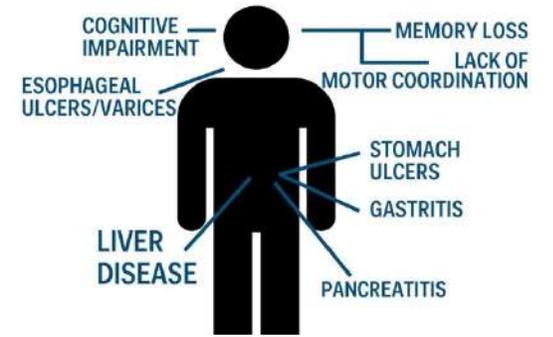


Alcohol misuse increases damage

- adverse effects on brain and behavior
- biological mechanisms are not well understood



Like HCV, chronic alcohol use affects not only liver function but also multi-organ interactions, contributing to impaired immune response, CNS inflammation and brain injury



Shared mechanisms underlying the pathological interactions between alcohol and HCV involve:

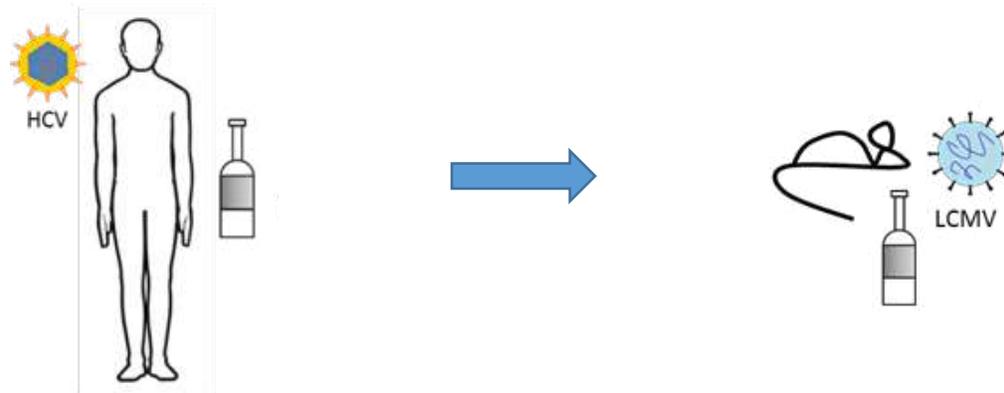
- 1) altered T cell responses,
- 2) compromised blood brain barrier function,
- 3) modulation of glial cell activation, cytokine production and immune signaling,
- 4) neuronal loss,
- 5) myelin damage, and
- 6) brain region-specific metabolic abnormalities (*e.g.*, altered levels of n-acetyl aspartate, choline, creatine, and myo-inositol)

The potential synergistic effects of a chronic viral infection and alcohol exposure on CNS pathology and behavior are not well defined.

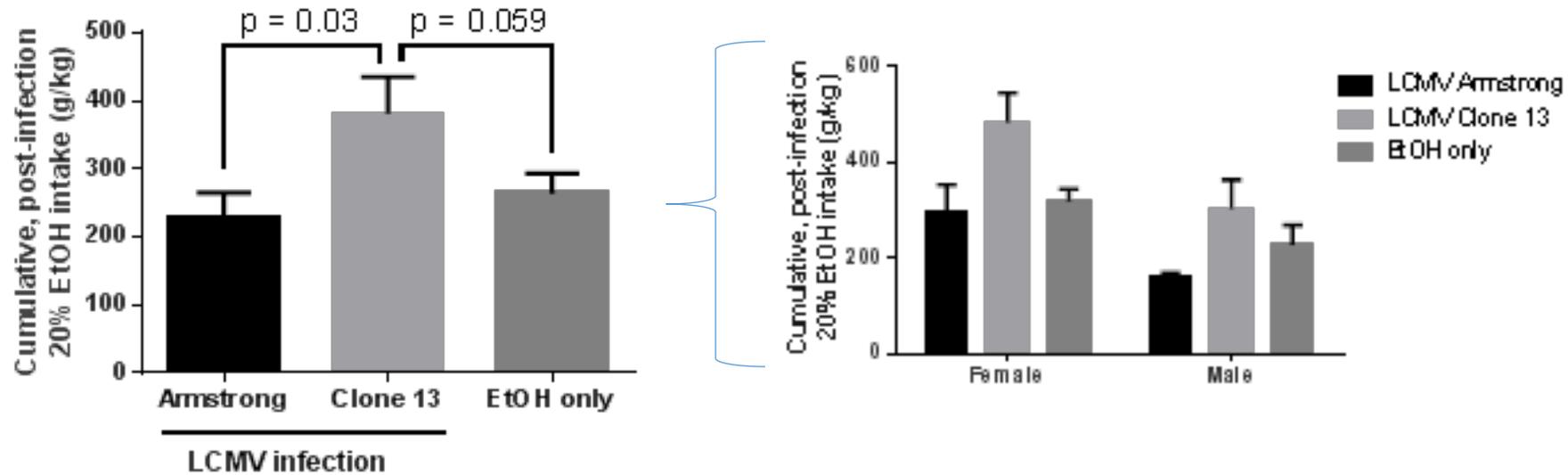


Research question...

What is the role of **alcohol** in **viral persistence** and **CNS damage**?



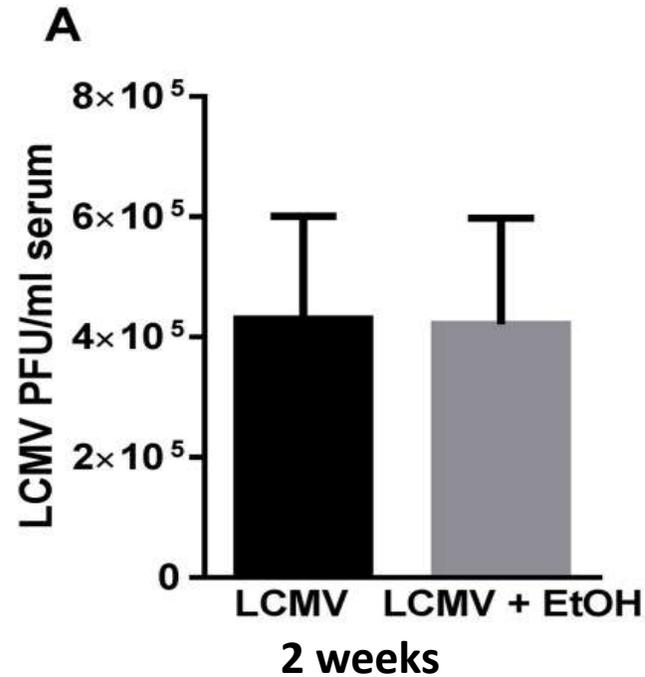
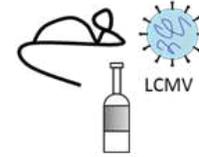
Mice infected with LCMV clone 13 exhibit increased alcohol consumption



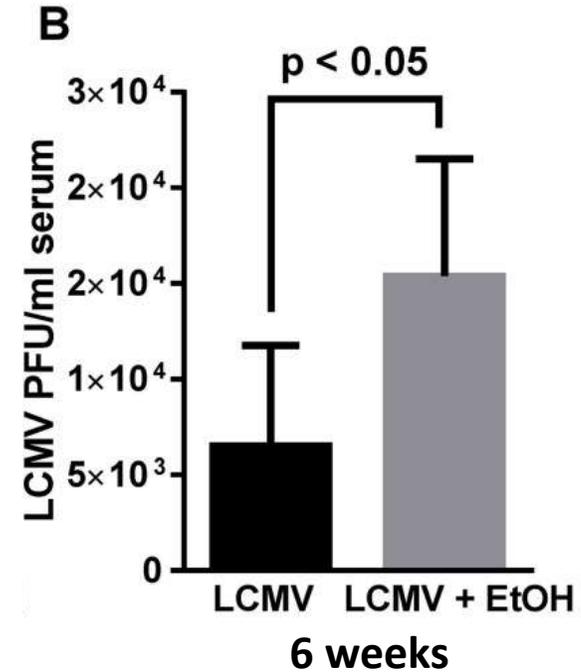
Adults who test positive for HCV report heavier alcohol intake than other adults

- 3 times more likely to consume an average of more than 1 drink per day, 35.3% vs. 13.5%
- ~ 8 times more likely to consume more than 3 drinks per day, 19.2% vs. 2.4%
- more likely to have had 5 or more drinks in a single day during the previous year than other adults, 47.8% vs. 27.7%

Alcohol exposure delays viral clearance in LCMV clone 13 infected mice

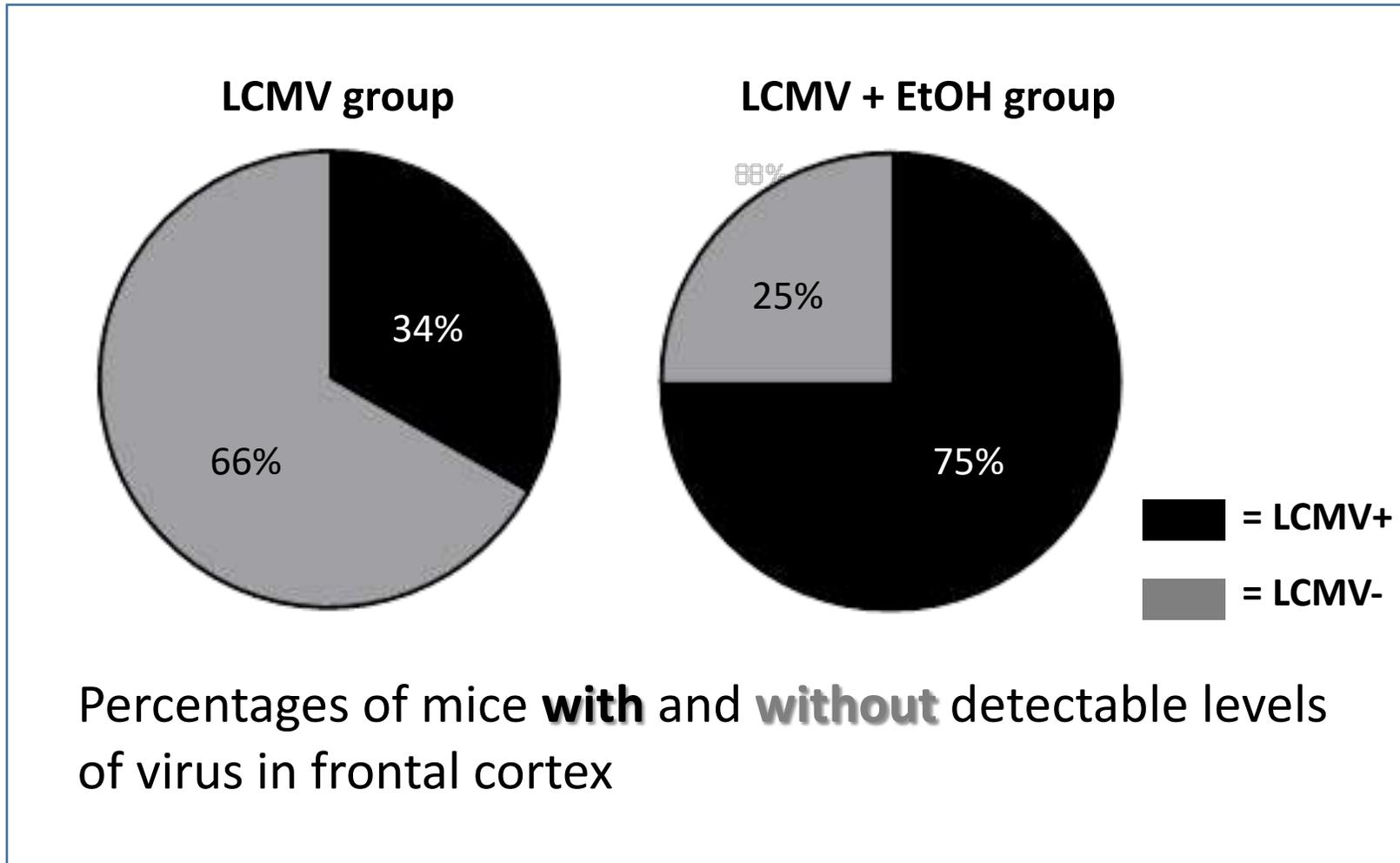
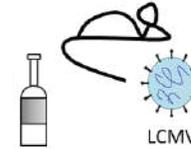


Two weeks following infection with LCMV, mice drinking alcohol (EtOH) had similar serum levels of virus, as compared to mice drinking water (LCMV only).



By six weeks post-infection, alcohol-drinking mice had higher viral levels, as compared to controls (LCMV only).

LCMV is more prevalent in brain from mice with a history of alcohol exposure



Novel object recognition test (NORT)

A. Training: In the first phase of the test, the mouse is allowed to explore two objects in order to get familiarized with the objects.

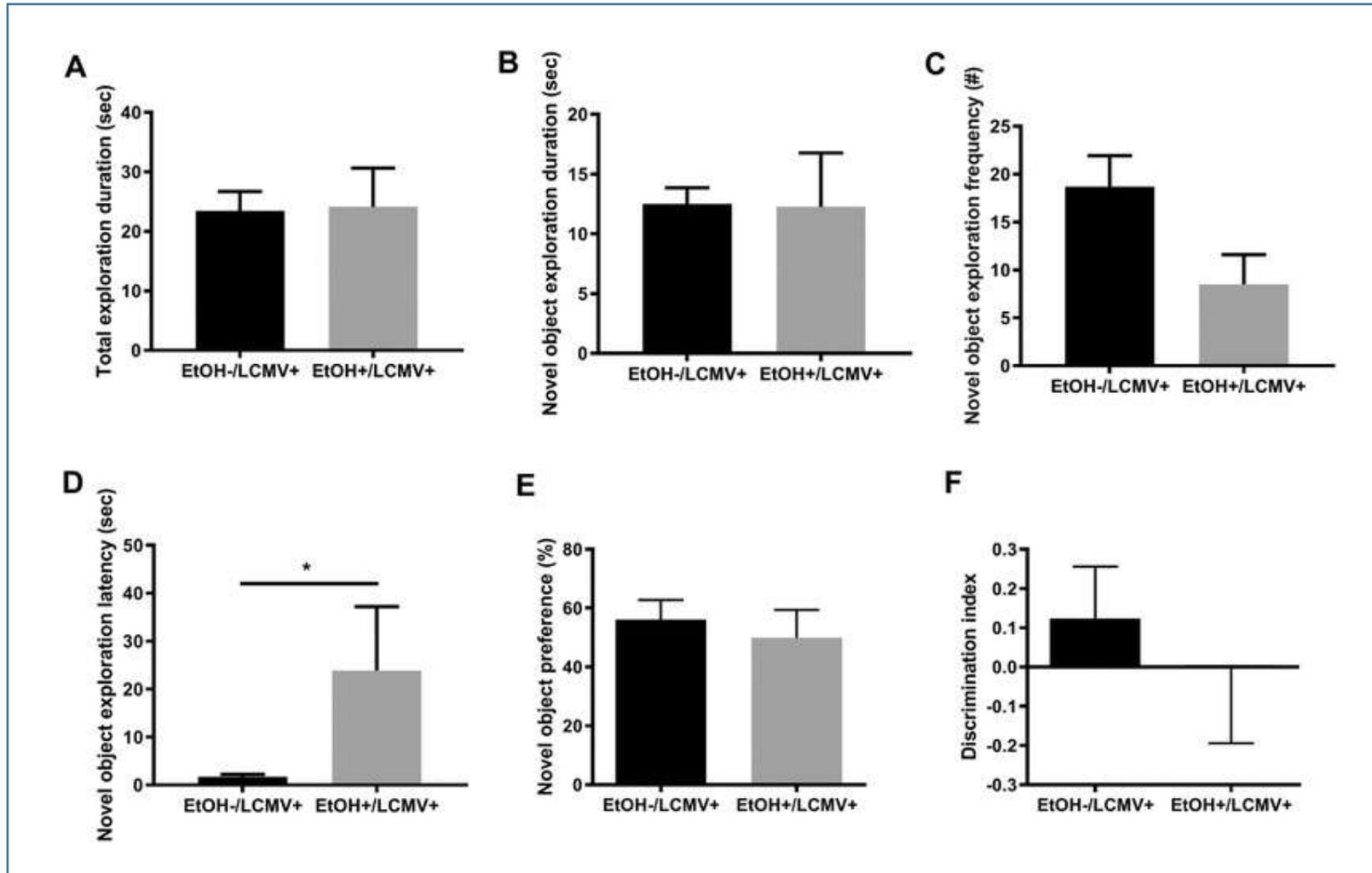
B. Retention: In the second phase, the mouse is exposed to two objects: one familiar object, used in the training phase, and one novel object.

During the retention session, the time spent exploring each of the objects is measured.

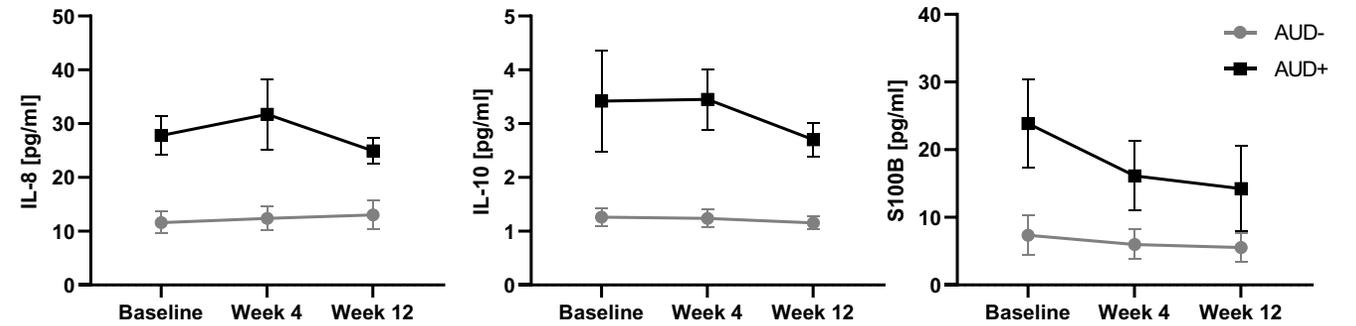
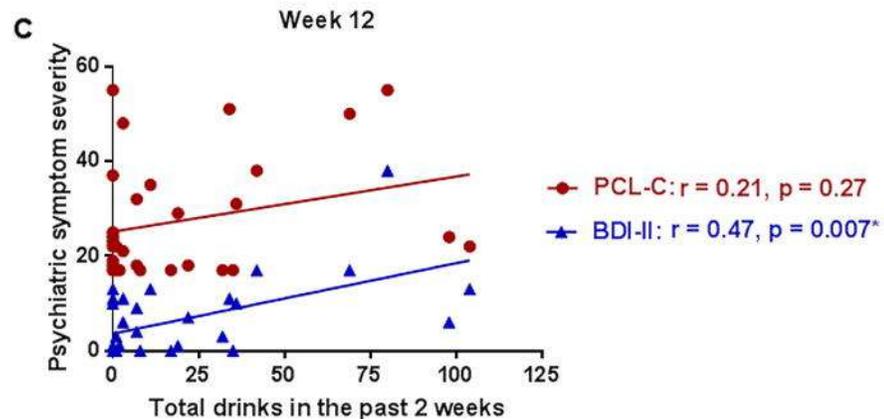
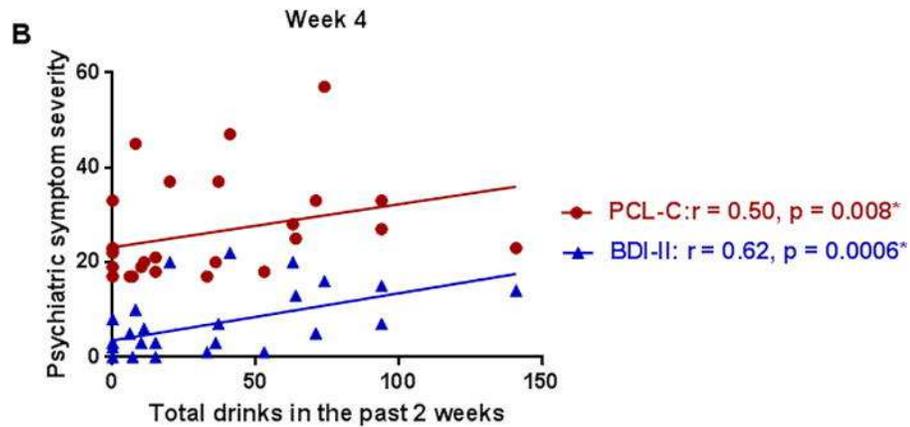
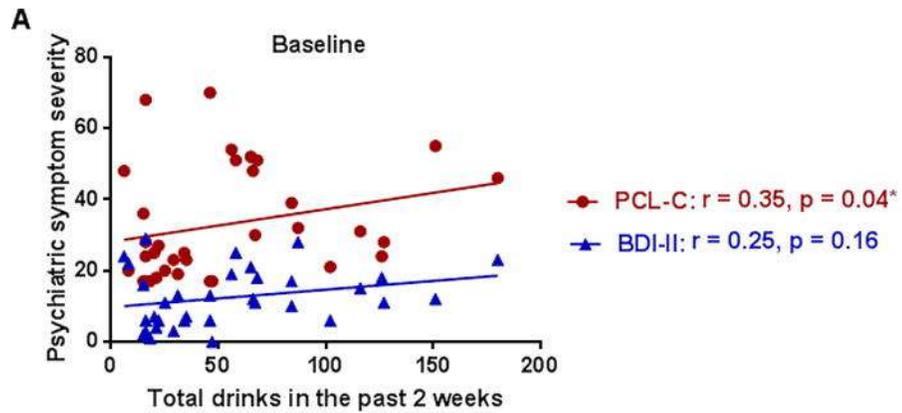


Mice without cognitive impairments will spend more time exploring the novel object than the familiar one.

Cognitive impairment associated with EtOH consumption during LCMV clone 13 infection

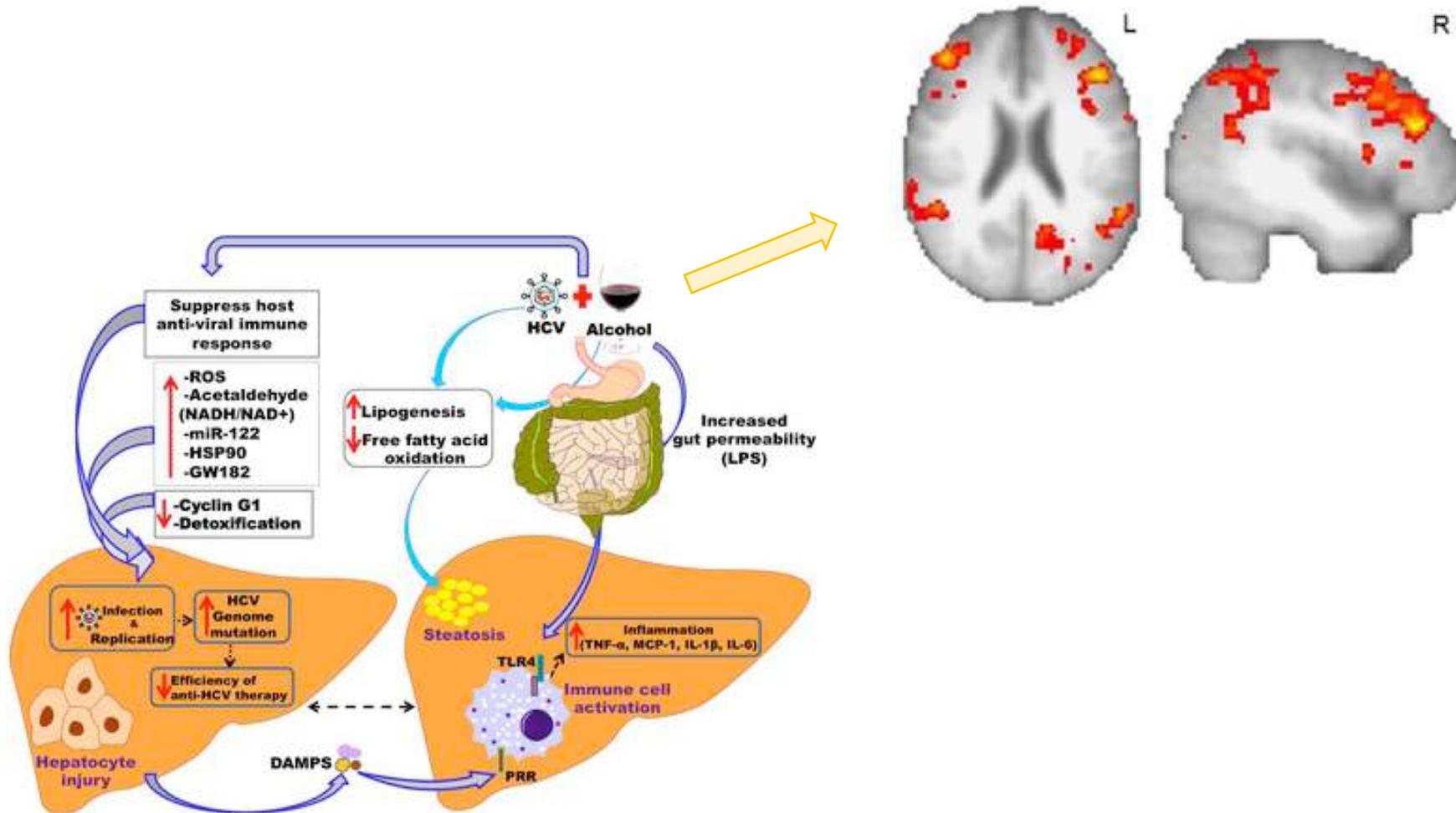


Level of alcohol consumption positively correlates with psychiatric symptom severity

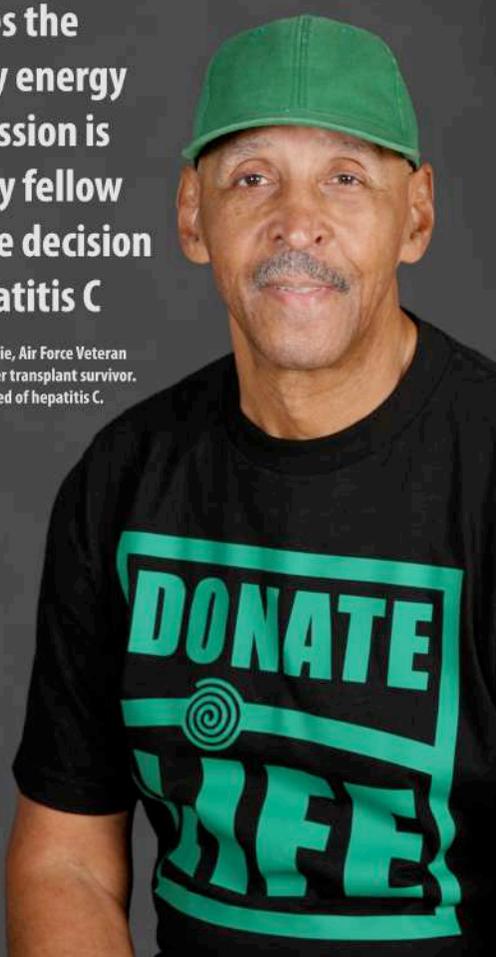


Blood plasma analyses identified significant group differences for IL-8, IL-10, and S100B, with increased levels in participants with AUD, which persisted over time despite reductions in alcohol use and no significant change in HCV viral load.

Interactions of HCV infection associated with alcohol use



“VA Extends New Hepatitis C Drugs to All Veterans in Its Health System”



VA is curing Hepatitis C

“Being cured improves the quality of my life. My energy level is up, my depression is gone. I encourage my fellow Veterans to make the decision to take the new hepatitis C treatments.”

Leslie, Air Force Veteran
Liver transplant survivor.
Cured of hepatitis C.

hepatitis.va.gov

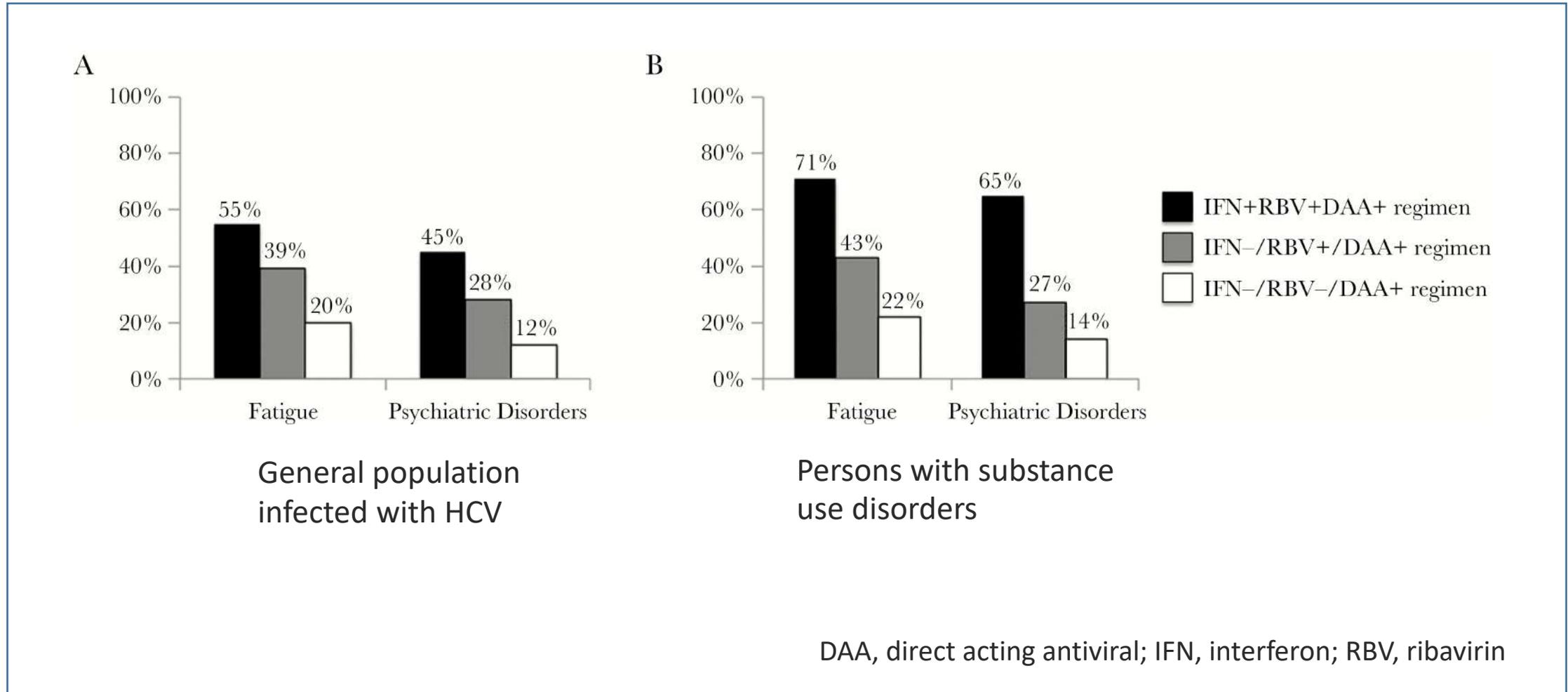
VA |  U.S. Department of Veterans Affairs
Veterans Health Administration
Patient Care Services

You must be enrolled in VA care to receive these services.

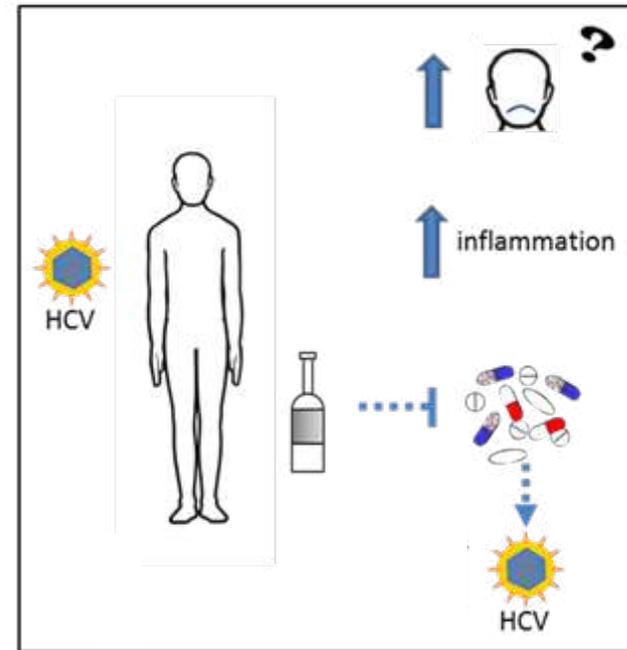
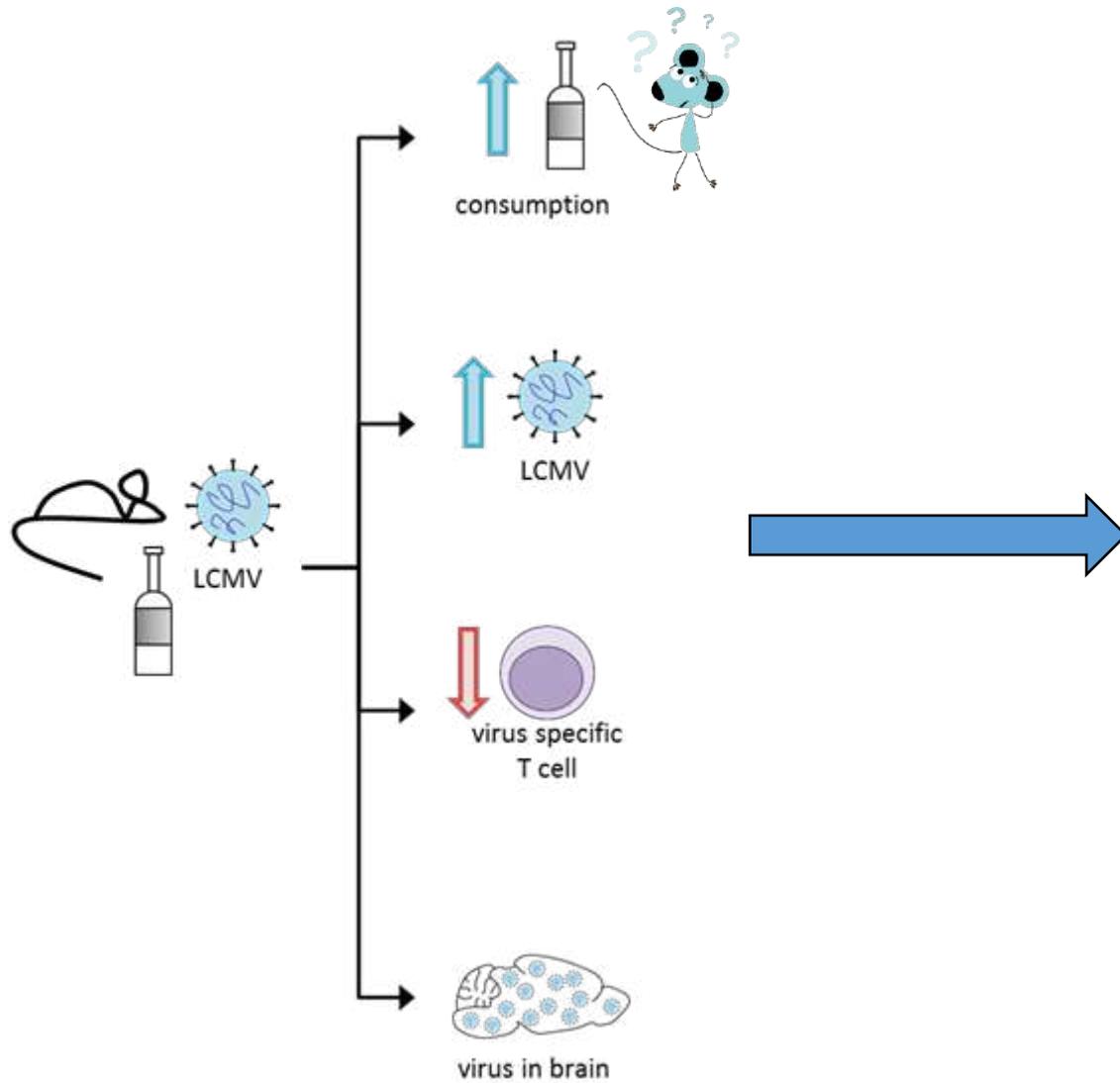
VA has reached a significant milestone in curing more than 100,000 Veterans of chronic HCV.

<https://blogs.va.gov/VAntage/64162/va-cured-100000-veterans-hepatitis-c/>

“Improvements in Quality of Life: A New Indication for Treating Hepatitis C Virus Infection in Persons With Substance Use Disorders”



Interim summary and next steps...



It is unknown whether viral clearance alone is sufficient to repair neuronal damage and improve brain function following chronic viral infection and in the context of heavy alcohol use.

Longitudinal cohort study to evaluate participants with HCV, with and without active AUD: anti-viral therapy outcomes

Two time points:

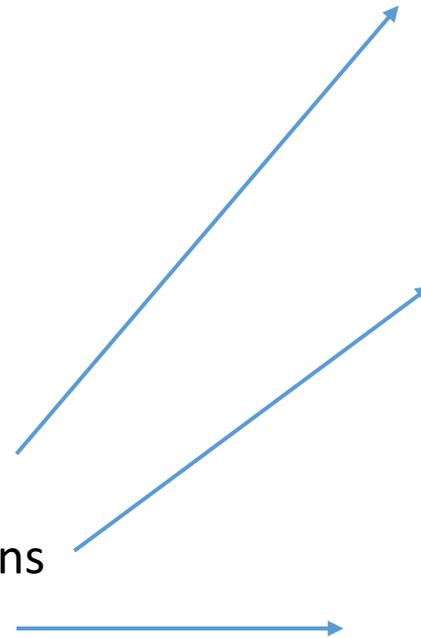
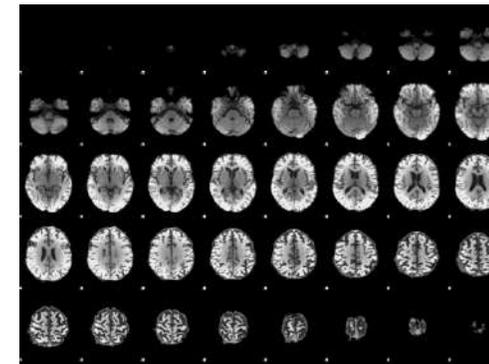
- i. baseline (prior to DAA therapy initiation)
- ii. 12 weeks post-therapy

Groups:

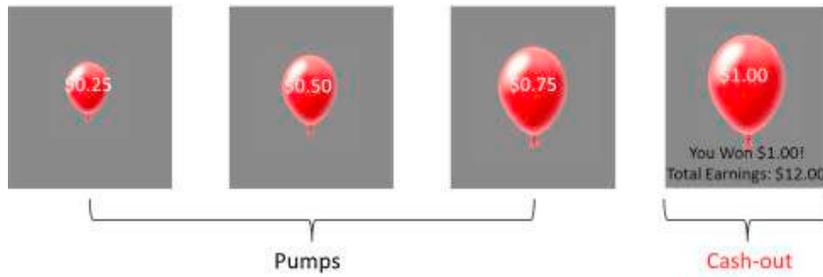
- i. AUD- and HCV-
- ii. AUD- and HCV+
- iii. AUD+ and HCV-
- iv. AUD+ and HCV+

Procedures:

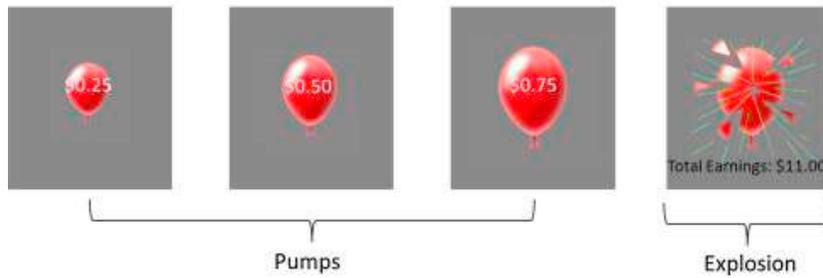
- neuropsychiatric evaluations
- biological specimen collections
- neuroimaging assessments



a) Cash-out trial



b) Explosion trial



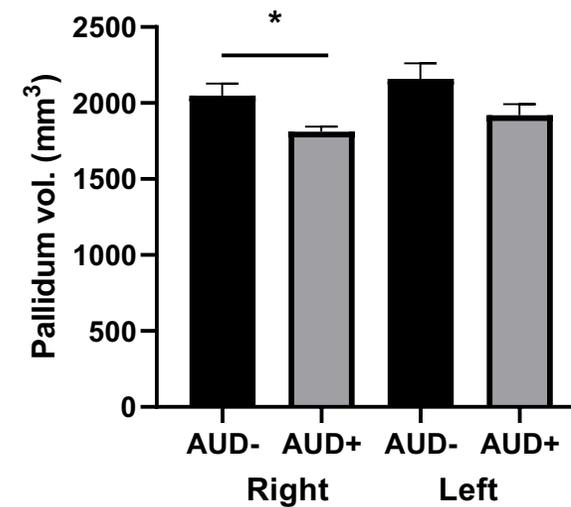
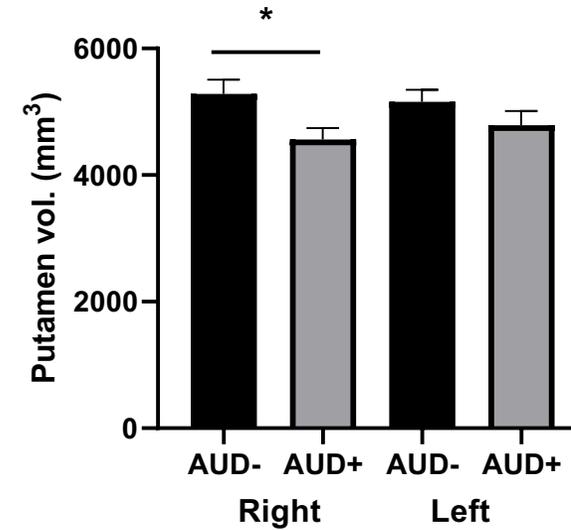
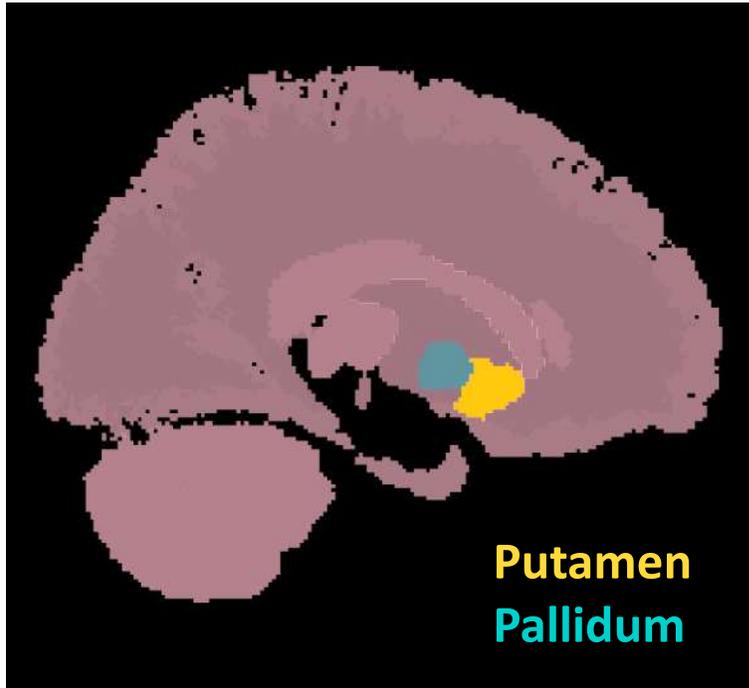
Balloon Analogue Risk Task (BART)



Monetary Incentive Delay (MID) task

Preliminary findings

Alcohol use disorder is associated with reductions in grey matter volume



Meth, the Forgotten Killer, Is Back. And It's Everywhere.

By FRANCES ROBLES FEB. 13, 2018

**The
New York
Times**



“Methamphetamine confiscated by the Portland Police Bureau in Portland, Ore. The drug, experts say, has never been purer, cheaper or more lethal.”

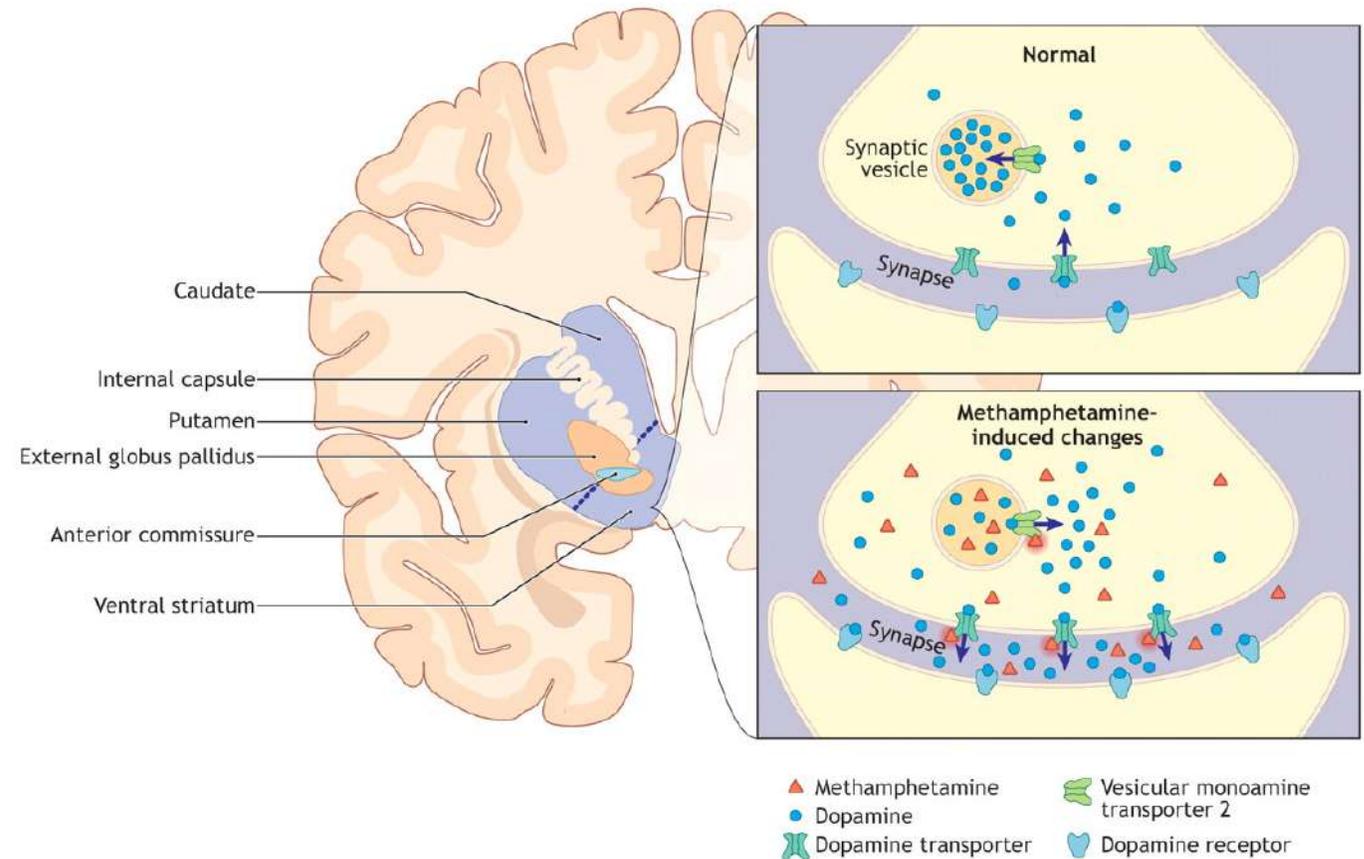
- Methamphetamine-related deaths in Oregon up 400%

While progress has been made to end the opioid crisis, the nation has seen a concerning increase in the use of deadly stimulants, with Oregon recently ranking second in the nation for methamphetamine use.

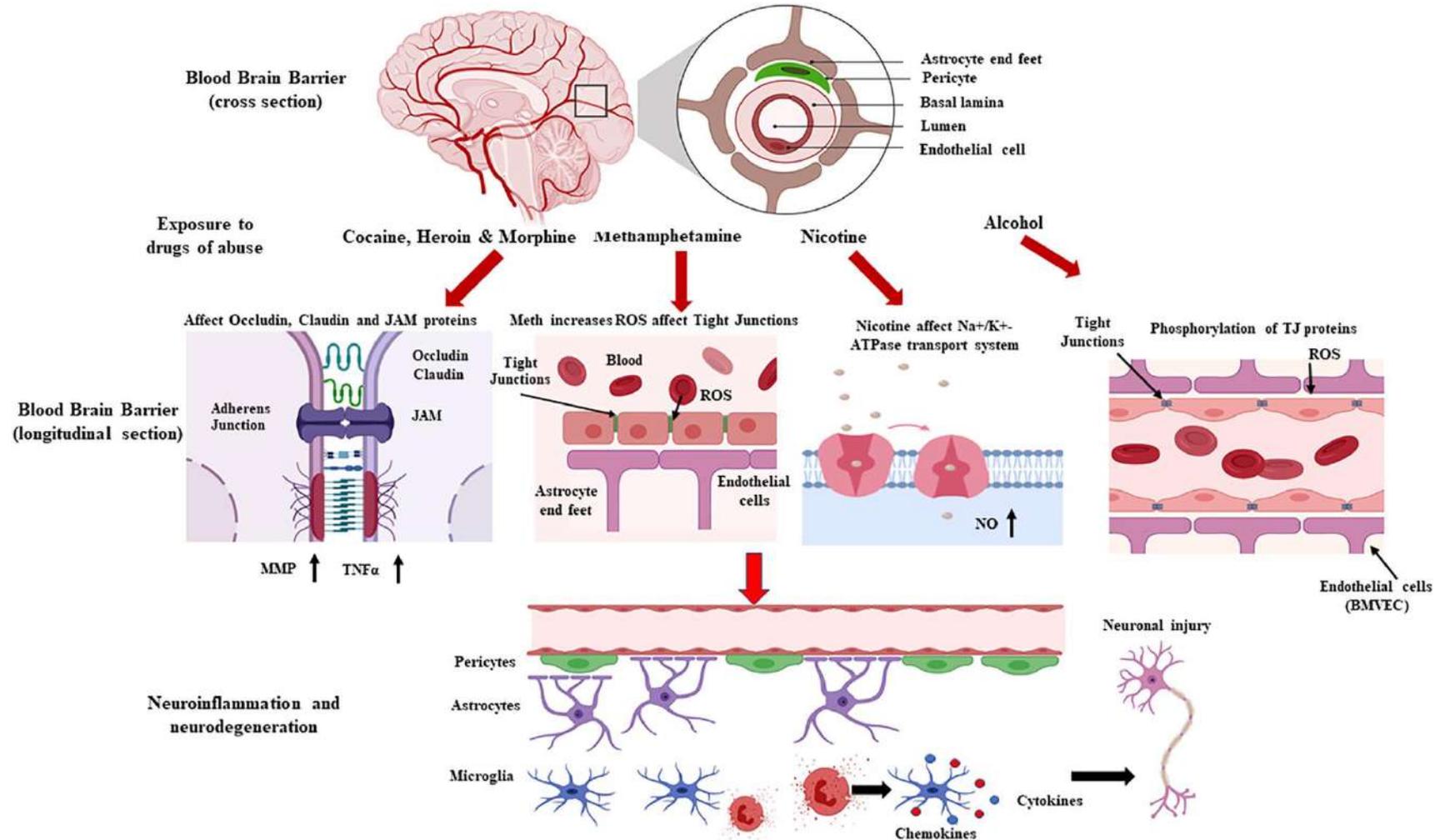
~ *Oregonian*, Feb. 5, 2020

Methamphetamine mechanisms of action

- Methamphetamine results in high levels of dopamine in areas that regulate the reward and other brain circuits



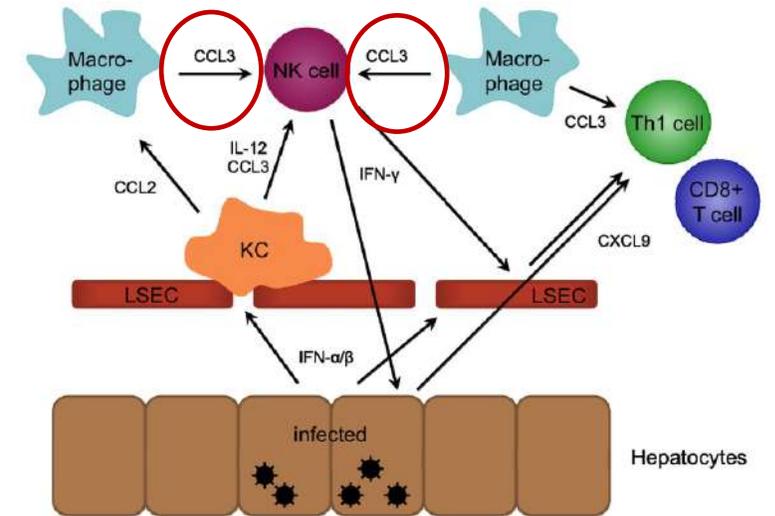
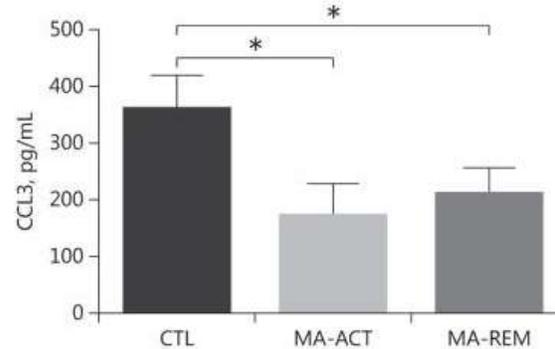
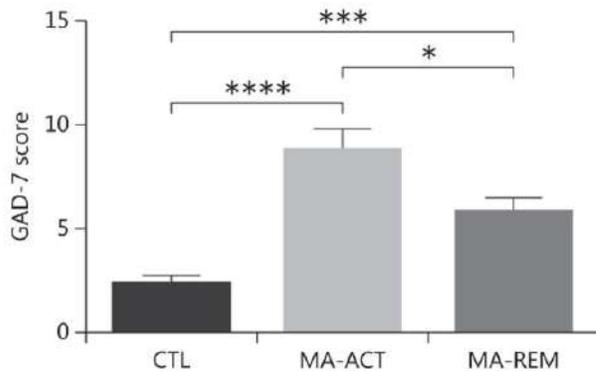
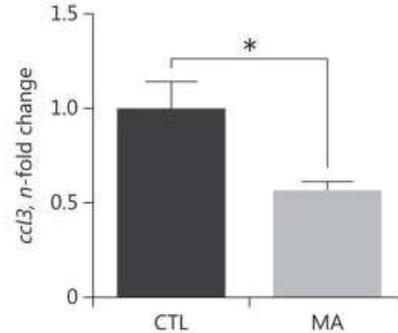
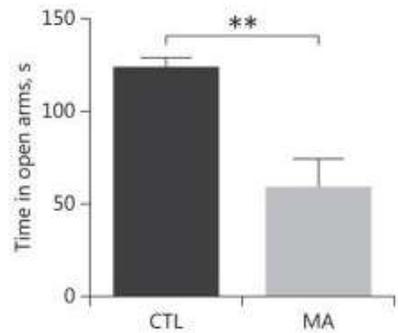
Drug-induced loss of blood brain barrier permeability



Parallel effects of methamphetamine on anxiety and CCL3



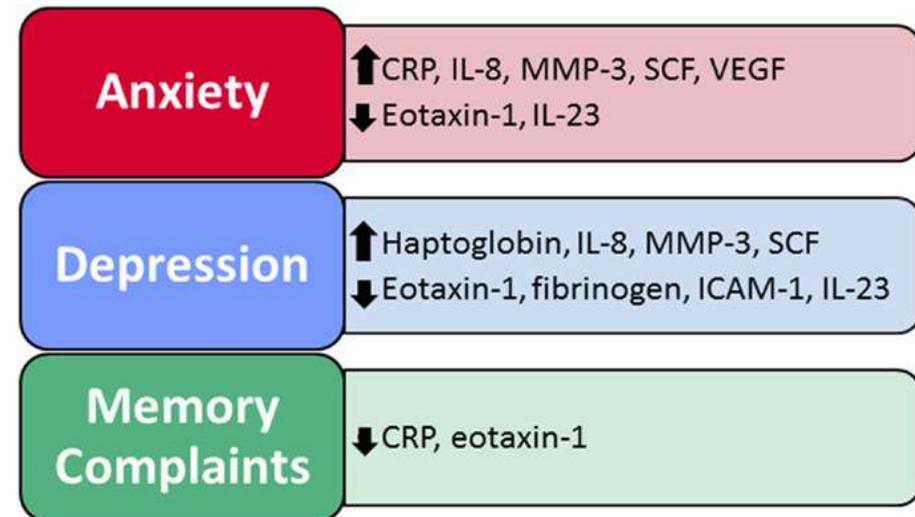
GAD-7 Score	Severity
0 - 5	None
6 - 10	Mild
11 - 15	Moderate
	Moderately Severe
16 - 21	Severe



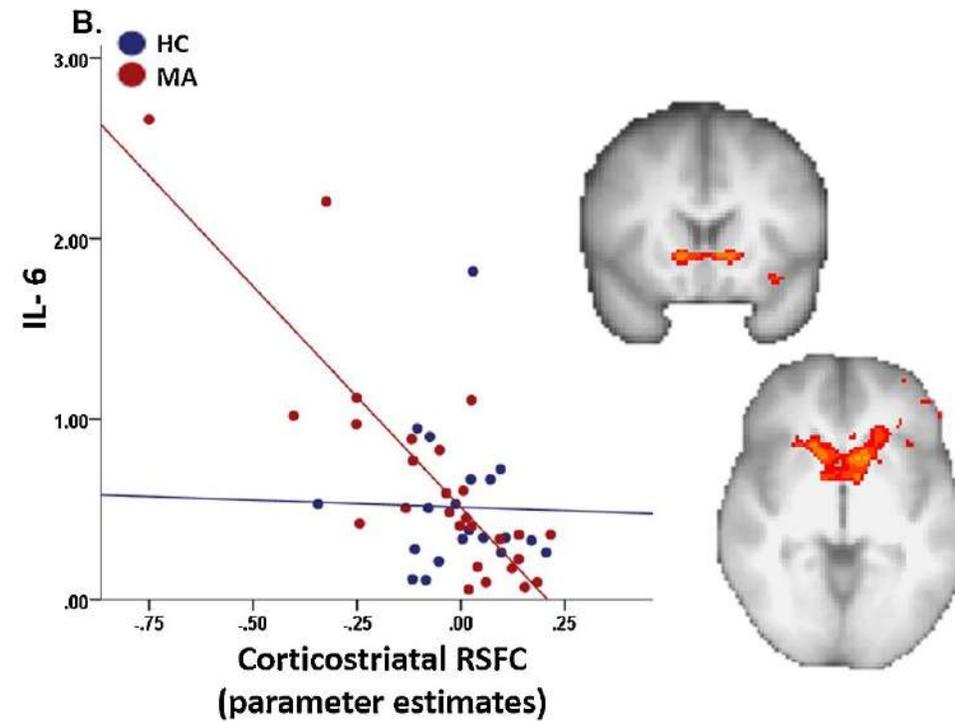
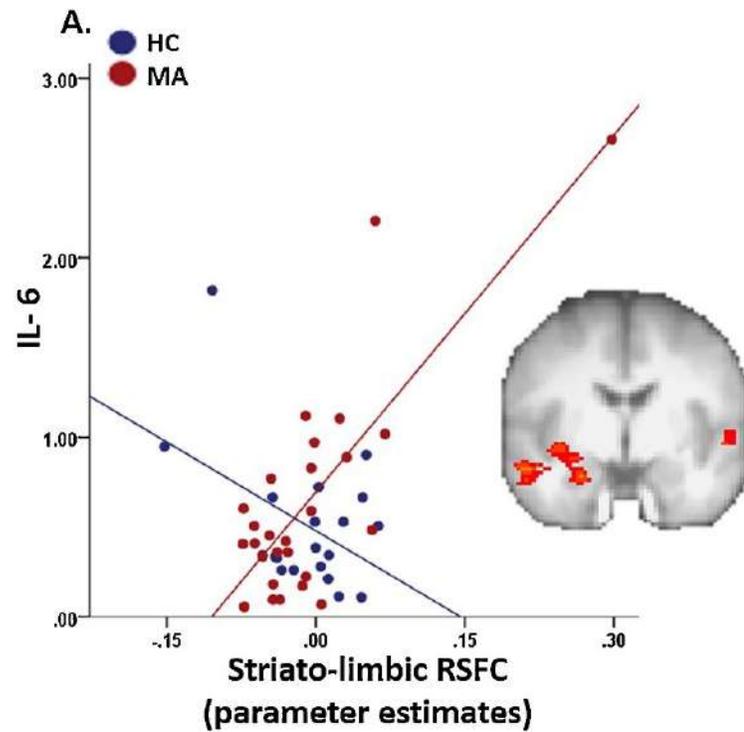
Methamphetamine-induced reductions in chemokine expression may impair HCV clearance

Immune factors predict self-reported anxiety, depression, and memory problems

- Two to eight immune factors were significant predictors of neuropsychiatric function.



IL-6 and functional connectivity in methamphetamine use disorder



Treatment strategies and future directions



HHS Public Access

Author manuscript

Addiction. Author manuscript; available in PMC 2015 May 05.

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Addiction. 2011 May ; 106(5): 1021–1022. doi:10.1111/j.1360-0443.2010.03354.x.

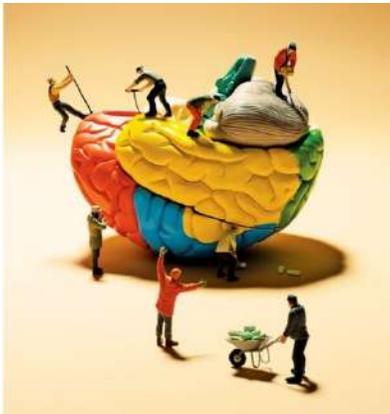
COGNITIVE ENHANCEMENT IN COMBINATION WITH ‘BRAIN REPAIR’ MAY BE OPTIMAL FOR THE TREATMENT OF STIMULANT ADDICTION

JENNIFER M. LOFTIS^{1,2} and **MARILYN HUCKANS^{1,2}**

JENNIFER M. LOFTIS: loftisj@ohsu.edu

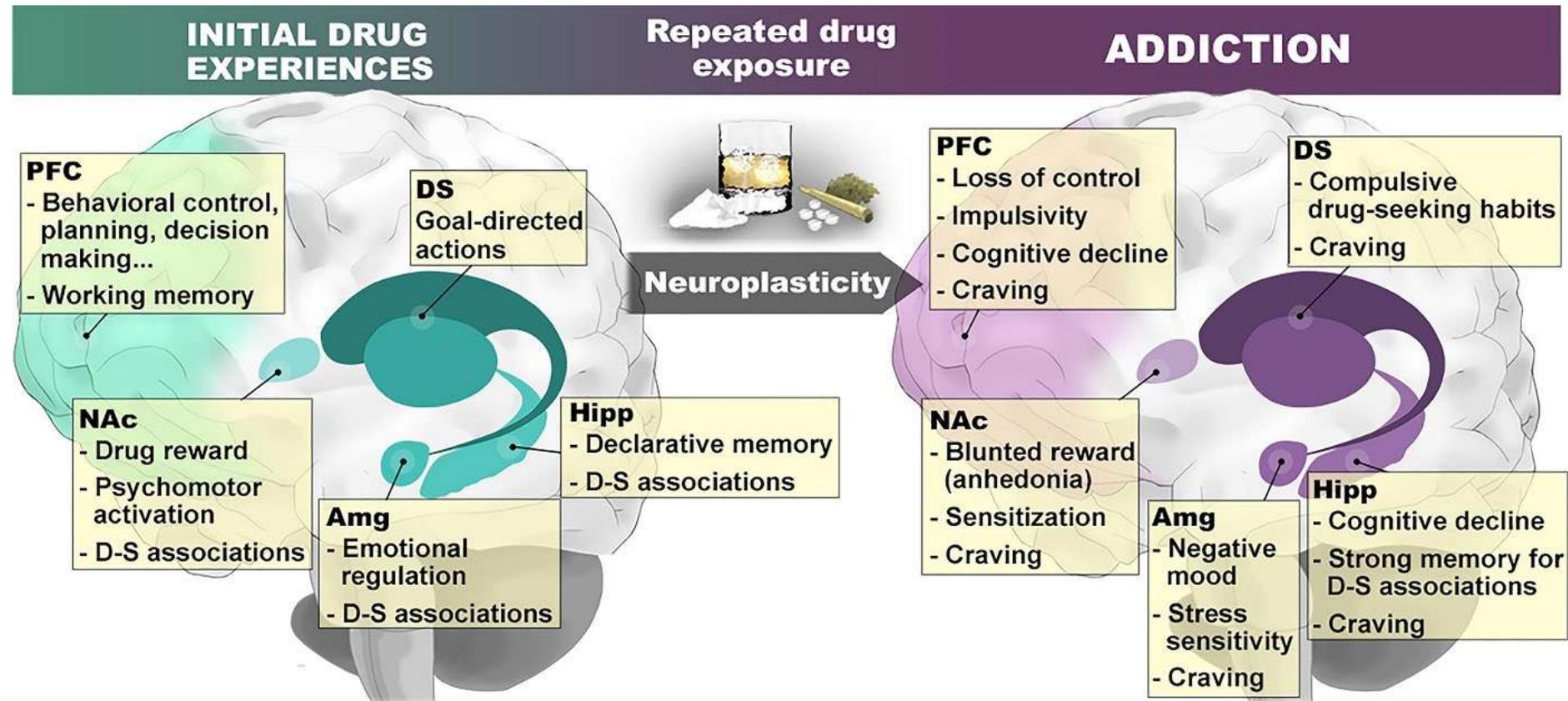
¹Research and Development Service, Mental Health and Clinical Neurosciences Division, Portland Veterans Affairs Medical Center, Portland, OR, USA

²Department of Psychiatry, Oregon Health and Science University, Portland, OR, USA

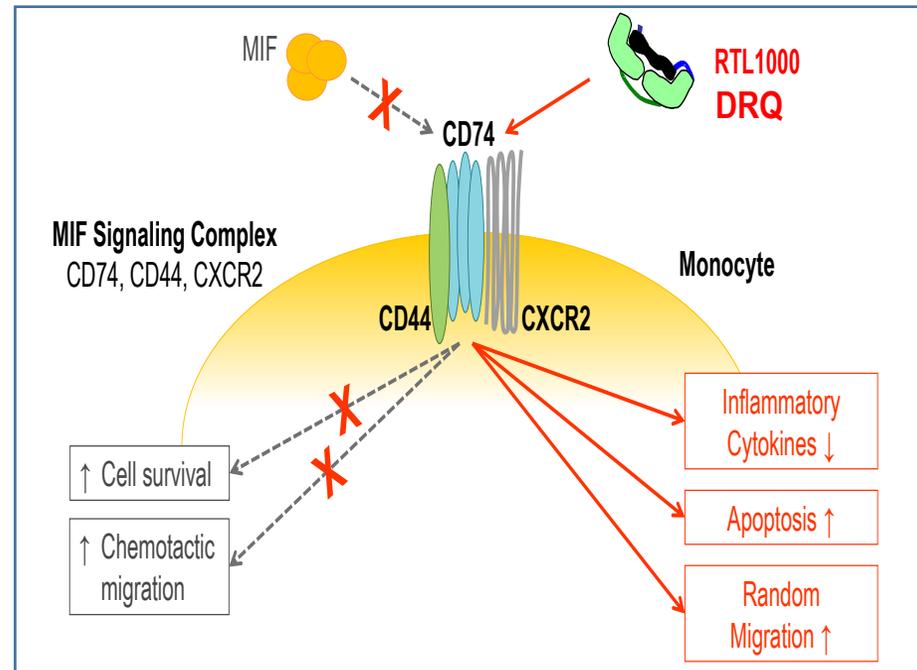
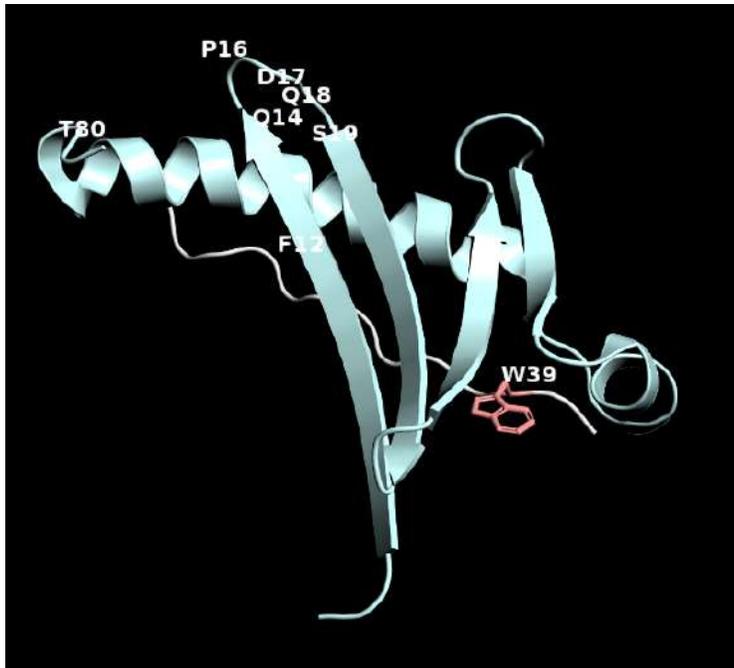


From brain repair to recovery...

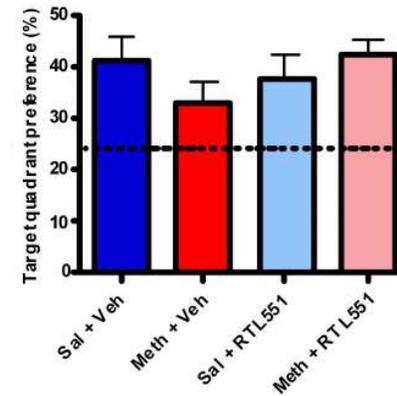
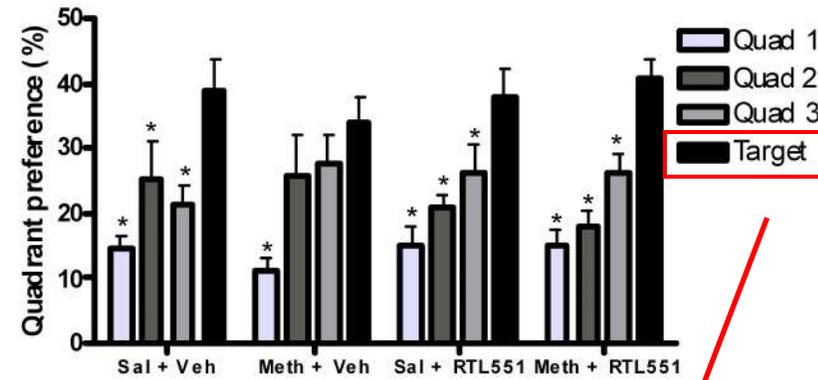
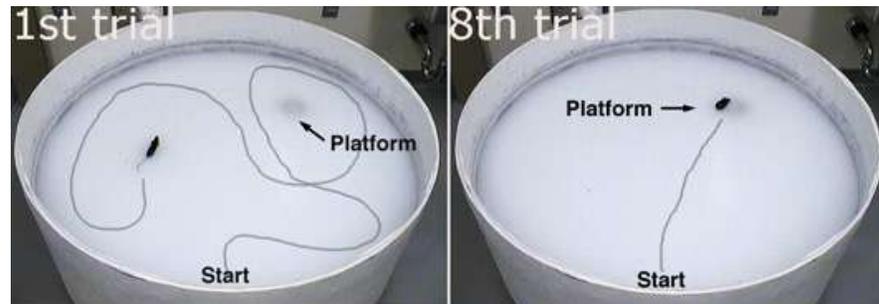
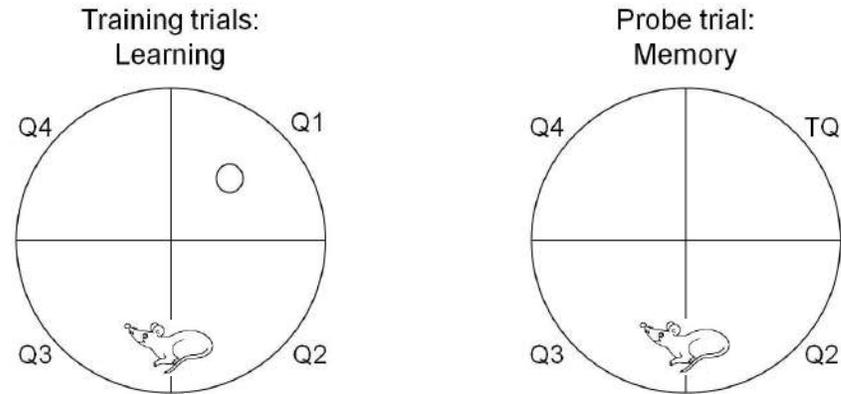
Brain circuits in addiction overlap with learning systems



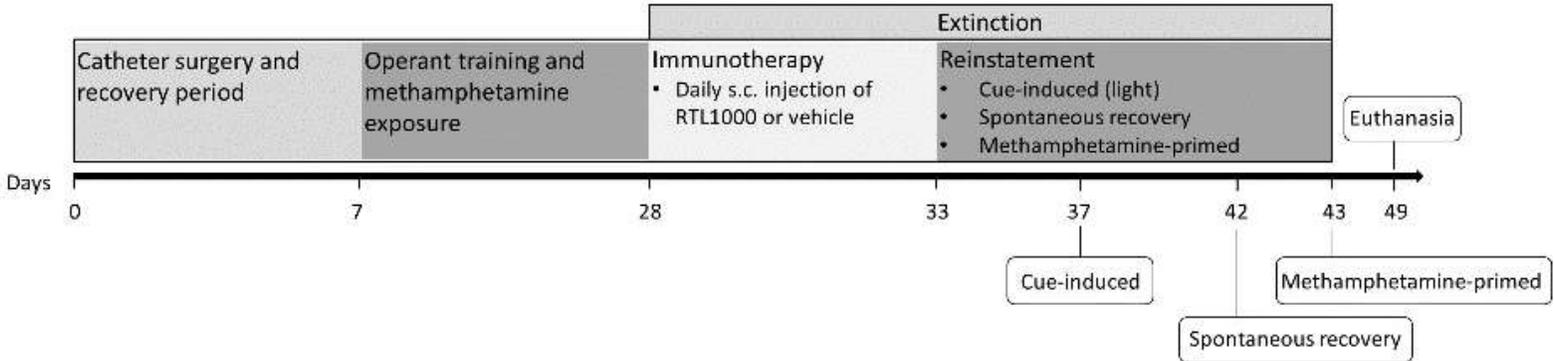
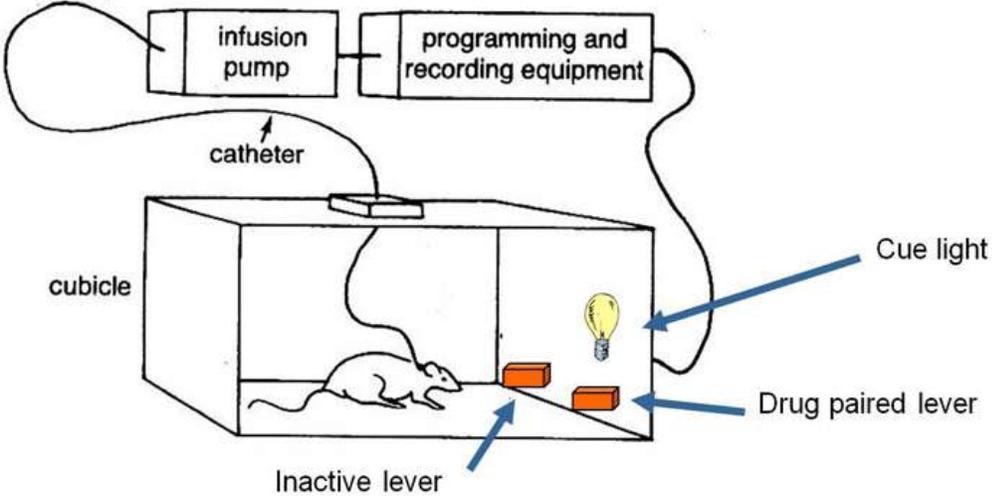
Immunotherapy development



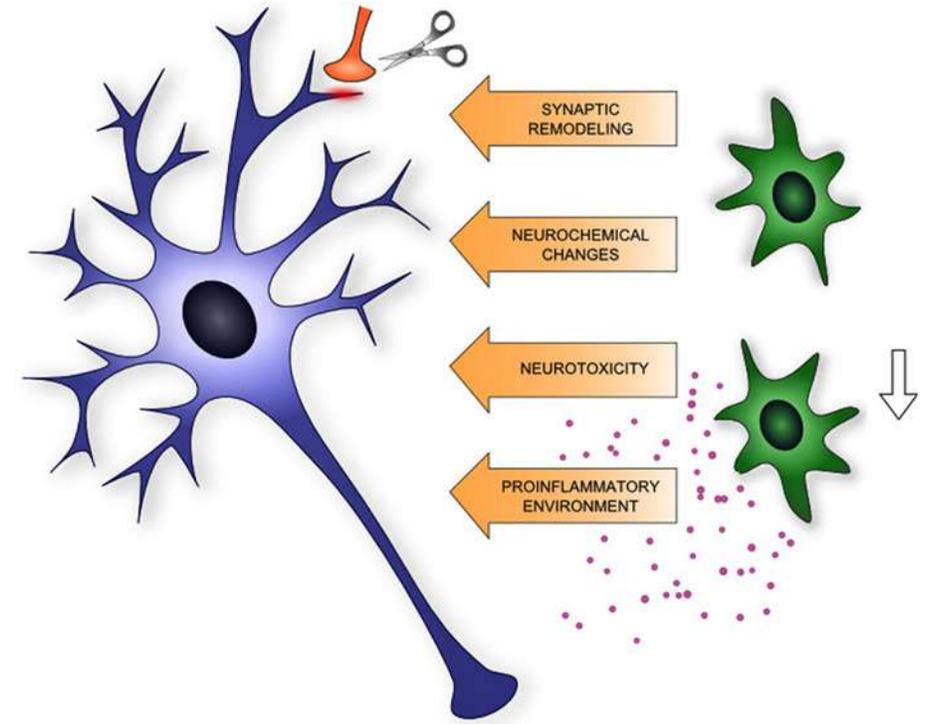
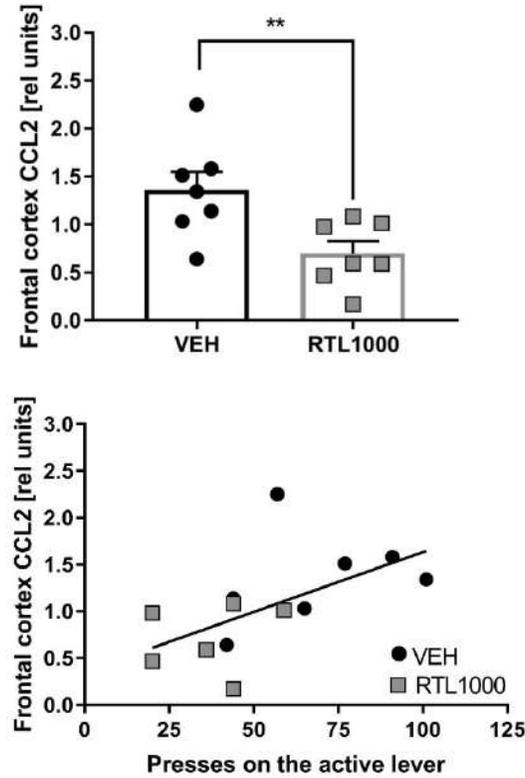
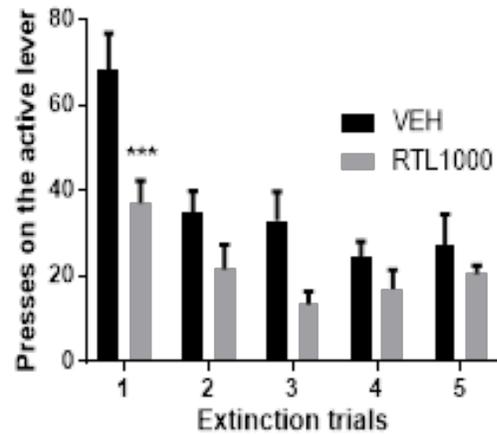
Methamphetamine and cognitive effects



Methamphetamine self-administration model

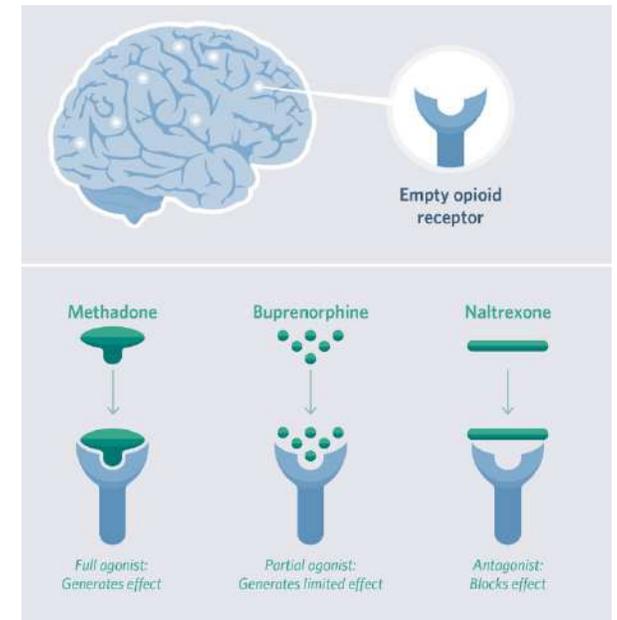


Drug seeking behavior and neuroinflammation



Evidence-based pharmacotherapies

- Reduce distress during acute withdrawal
- Antagonists that block drug rewards
- Medications that produce adverse reactions to a substance
- Agonists that mimic drug effects
- Medications that treat psychiatric symptoms



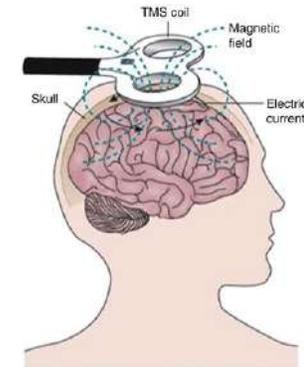
FDA-approved drugs

Pharmacotherapy	Clinical indication	Mechanism of action
Disulfiram	Prevention of relapse to alcohol use	Ethanol metabolism inhibition
Methadone	Opioid substitution therapy	Full opioid receptors agonism
Nicotine replacement therapies	Tobacco smoking substitution therapy	Full nicotinic receptors agonism
Naltrexone	Drinking reduction and prevention of relapse	Opioid receptors antagonism
Bupropion	Anti-craving drug; Relapse prevention for tobacco smoking	Dopamine and noradrenaline re-uptake blocker Nicotinic receptors antagonism
Buprenorphine	Opioid detoxification therapy	Partial opioid receptors agonism
Acamprosate	Relapse prevention for AUD	Partial glutamate receptors agonism
Nalmefene	Drinking reduction	Partial opioid receptors agonism
Varenicline	Relapse prevention in for tobacco smoking	Partial nicotinic receptors agonism

Medications have targeted neurotransmitter systems

Research groups are currently testing other approaches...

- Vaccine and monoclonal antibody therapies
- Anti-inflammatory therapies
- Neuromodulation
- Exercise



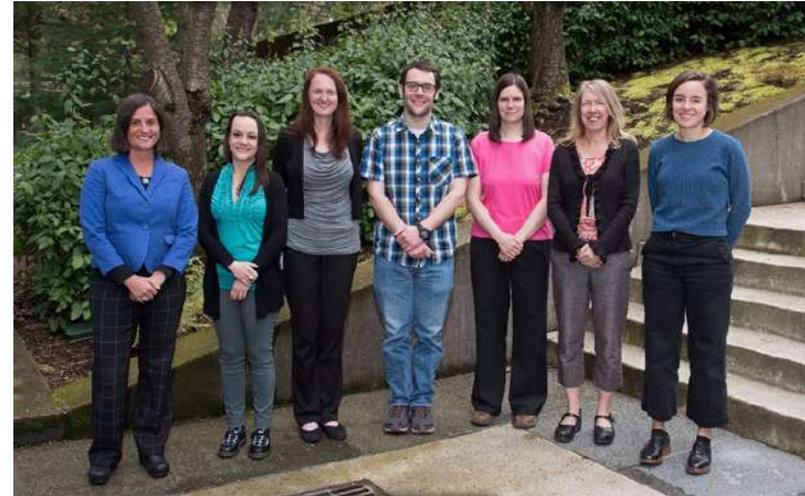
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Psychoneuroimmunology Research Team
<http://www.ohsu.edu/pniresearch>

Methamphetamine Research Center (MARC)
<http://www.ohsu.edu/marc/>



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Psychoneuroimmunology Research Team

<http://www.ohsu.edu/pniresearch>

Methamphetamine Research Center

<https://www.ohsu.edu/methamphetamine-research-center>