Alcohol: Systems Biology

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Alcohol is Unique

Weak drug: intoxication at 10-50 mM

- Interacts with multiple signaling molecules
- Disrupts virtually all organ systems across the life span
- Effects in one organ system modify function of others

Metabolism yields 7 kcal/gm, toxic acetaldehyde, and reactive oxygen species.

- Replaces food calories; malnutrition; organ toxicity; cancer

Ubiquitous, socially acceptable, recreational drug used with health benefits by more than 120 million Americans.

- Moderate drinking decreases risk of heart disease, stroke, dementia

Alcohol Abuse and Dependence: 100,000 deaths; $200 Billion

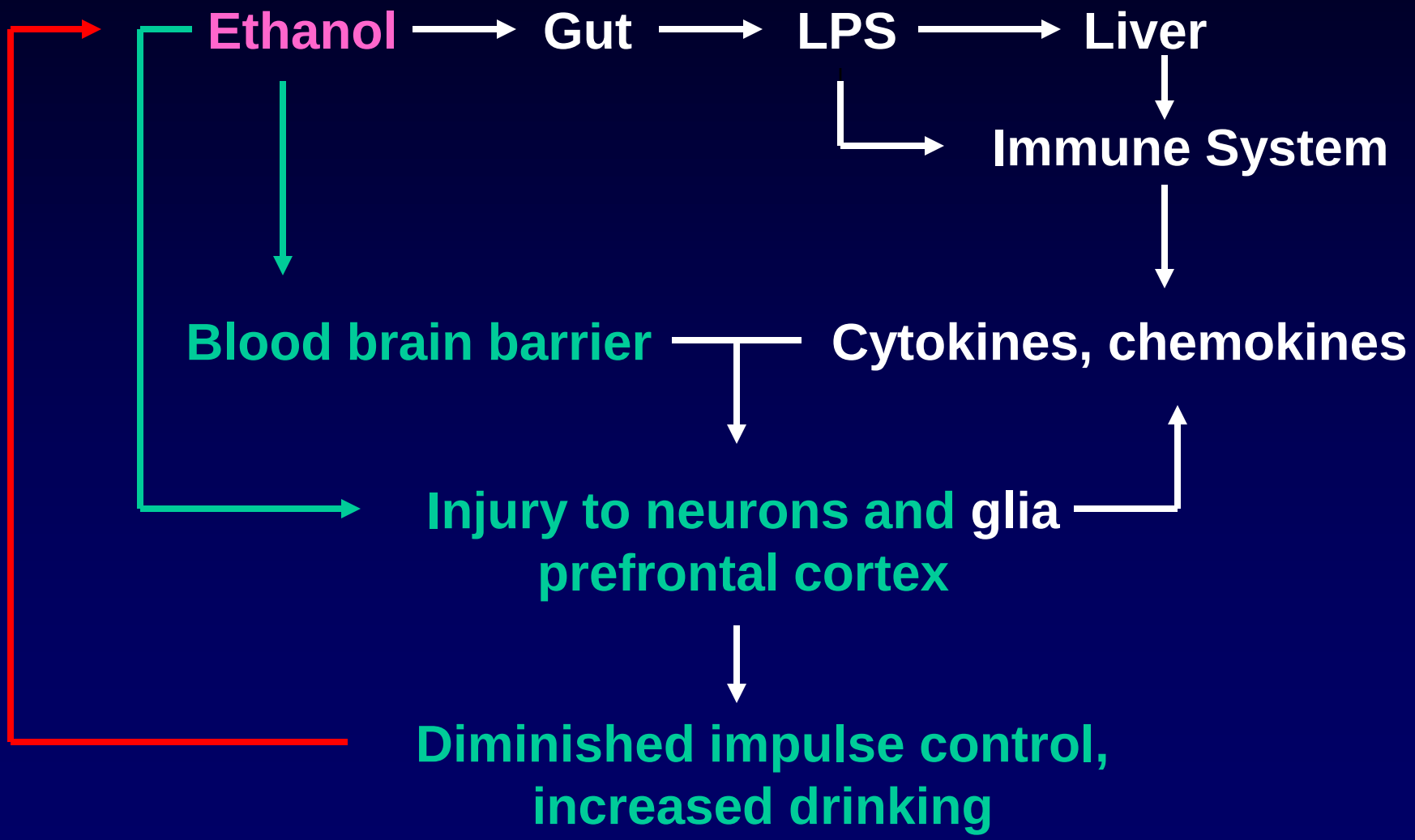
Abuse (Intermittent heavy use; binge drinking)

- Traffic fatalities (1/3); suicide (1/2); murders (1/2); sexual assault; risky sexual behavior; domestic violence; accidents; lost productivity; FASD; liver disease; stroke; intracerebral hemorrhage; pancreatitis; alcohol poisoning

Dependence (Regular heavy use).

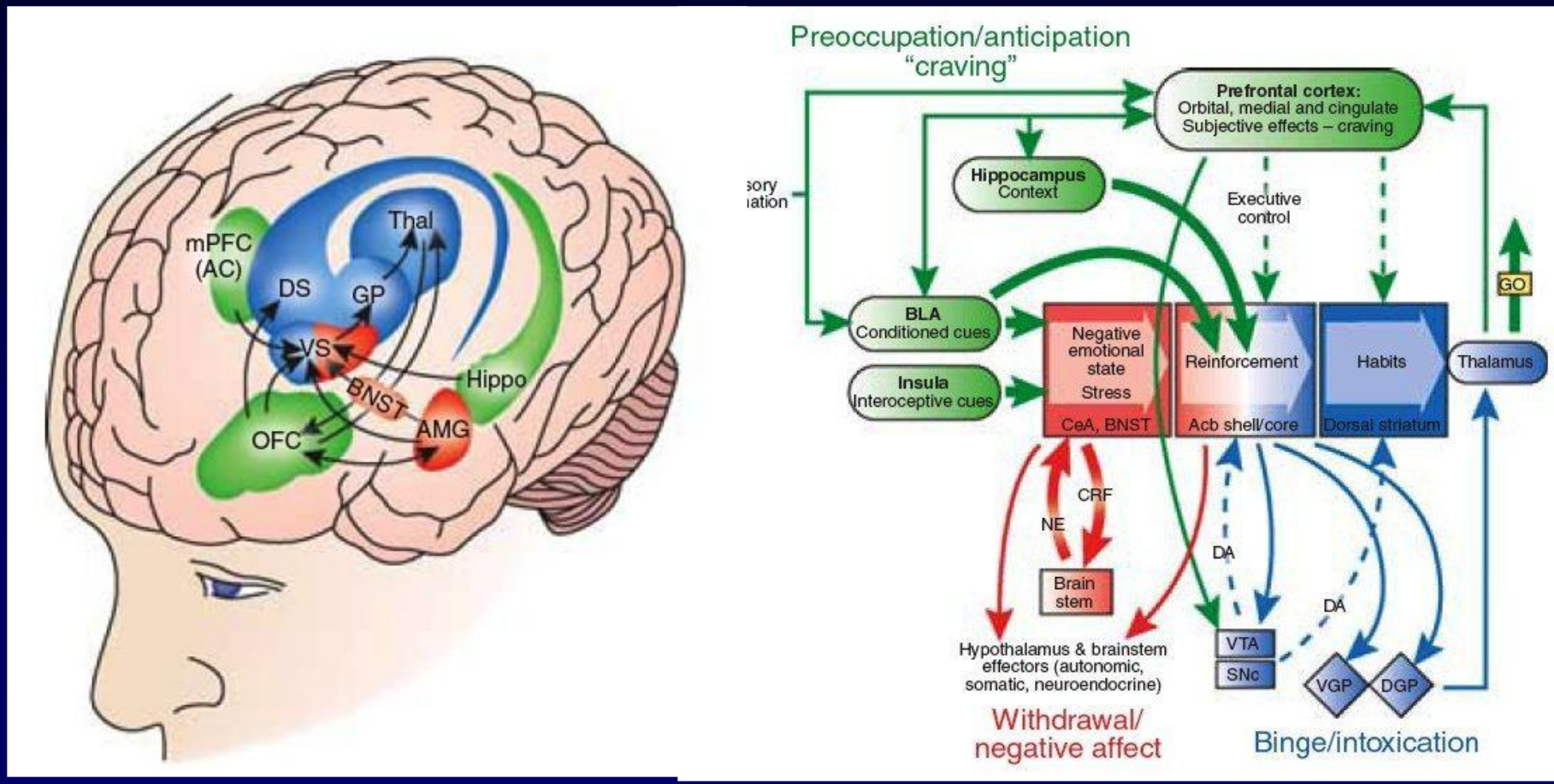
- FASD, dementia, neuropathy, cardiomyopathy, myopathy, cirrhosis, pancreatitis, gastritis; immunocompromise; cancer, alcohol withdrawal syndrome, seizures, and DTs

Organ Damage and Addiction are Impacted by Ethanol Effects on Multiple Organ Systems



Brain Circuits that Regulate Addictive Behavior

Koob and Volkow, Neuropsychopharmacology, 2009



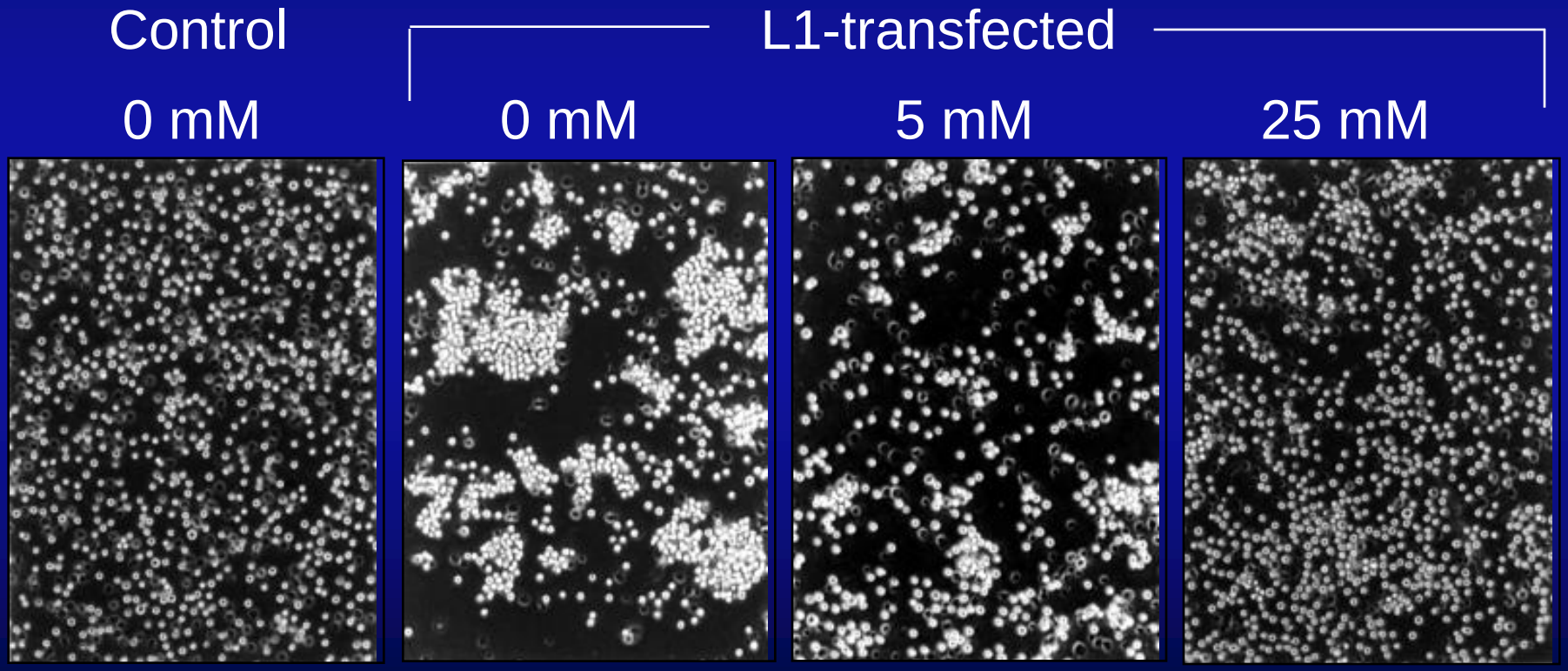
Fetal Alcohol Spectrum Disorders

- Deficient brain growth and dysmorphology
- Prenatal and/or postnatal growth retardation
- Facial dysmorphology

Most common non-genetic cause of mental retardation

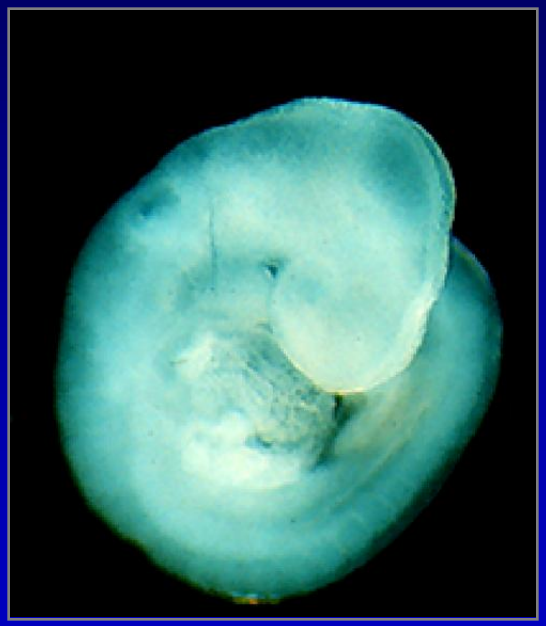
In-School Prevalence	
FAS:	0.2 - 0.7%
FASD:	2 - 5%

Ethanol inhibits cell adhesion in L1-transfected mouse L cells.

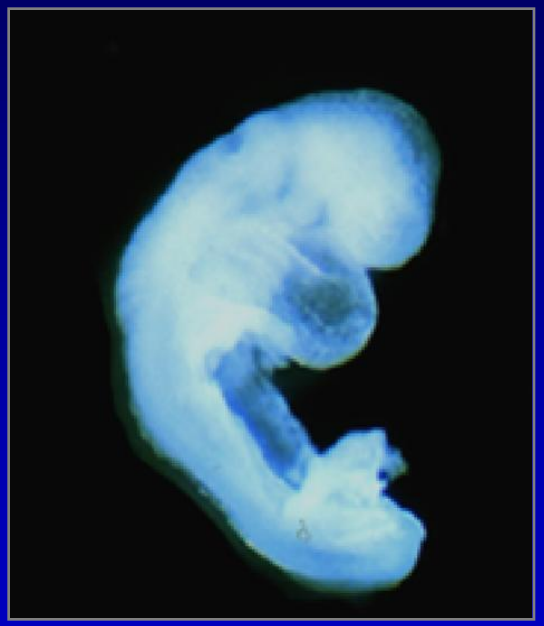


Ethanol does not inhibit cell adhesion in N-CAM transfected cells.

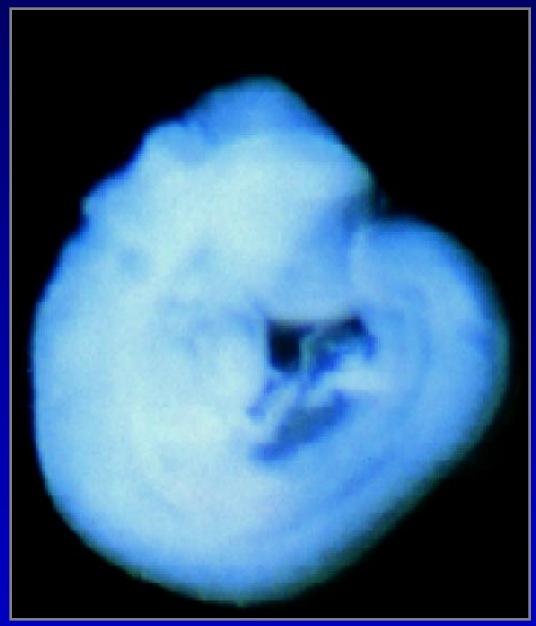
Drugs that block ethanol effects on L1 also prevent ethanol teratogenicity in mice



CONTROL

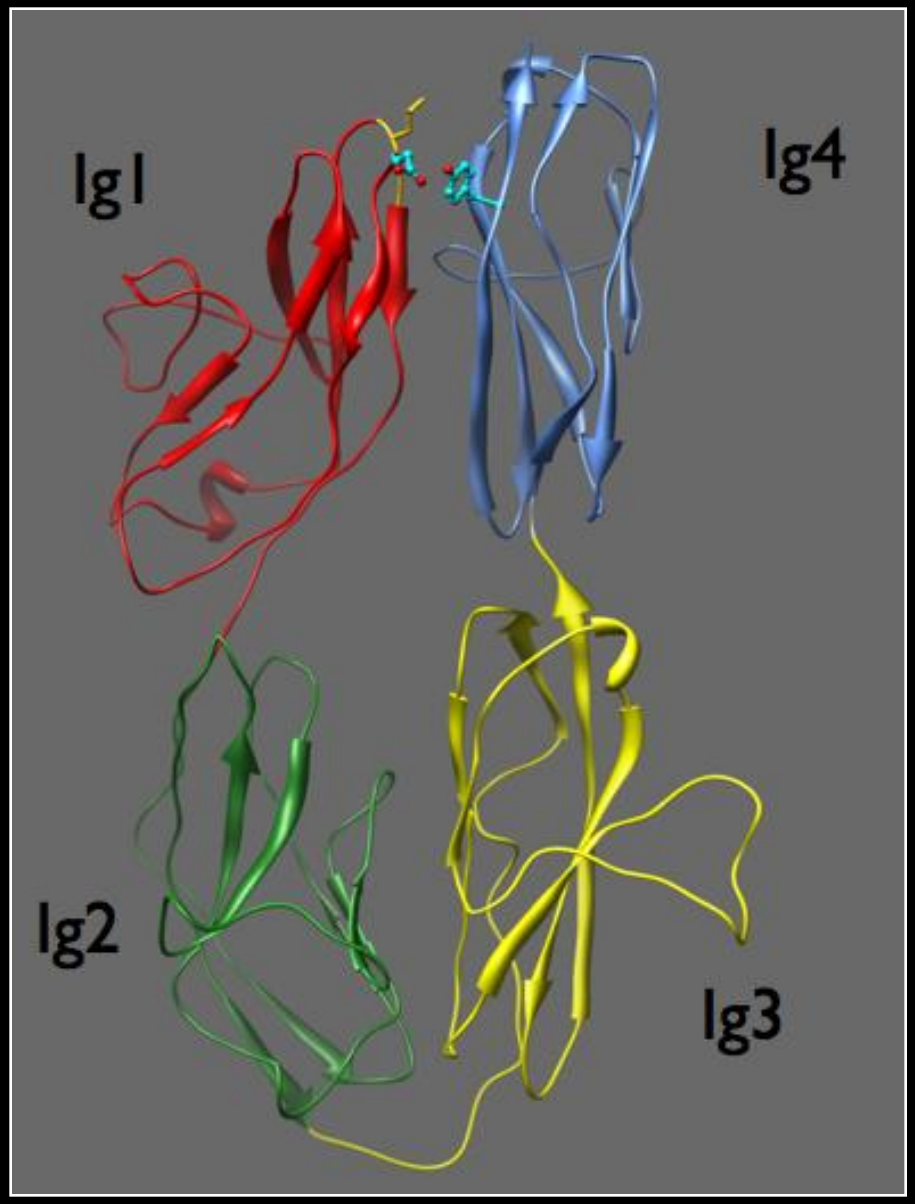


ETOH

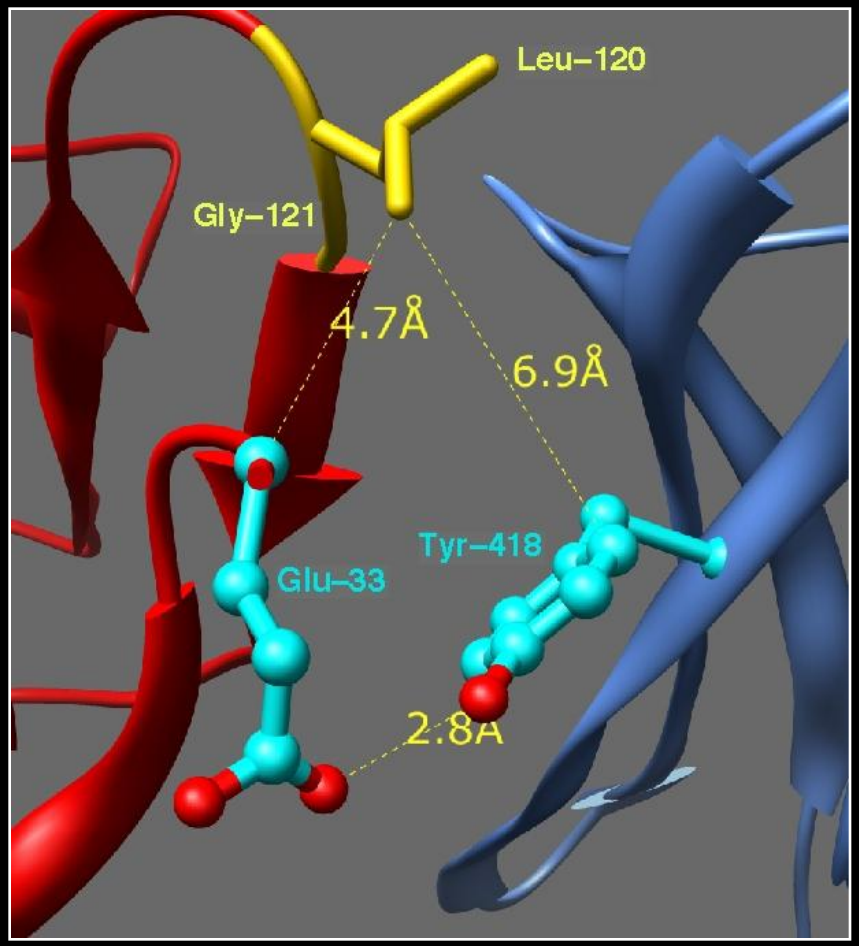


ETOH/OCT

Photos depict median number of somites per group.



Arevalo et al, PNAS, 2008



Photolabeling identifies a binding pocket for alcohol agonists and antagonists at the domain interface between Ig1 and Ig4, The two photolabeled residues, Tyr-418 and Glu-33, form a strong hydrogen bond between the Ig1 and Ig4 domains close to Leu-120 and Gly-121, at which mutation causes human disease similar to FAS.

Fetal Alcohol Spectrum Disorders: Spectrum of NIAAA Research

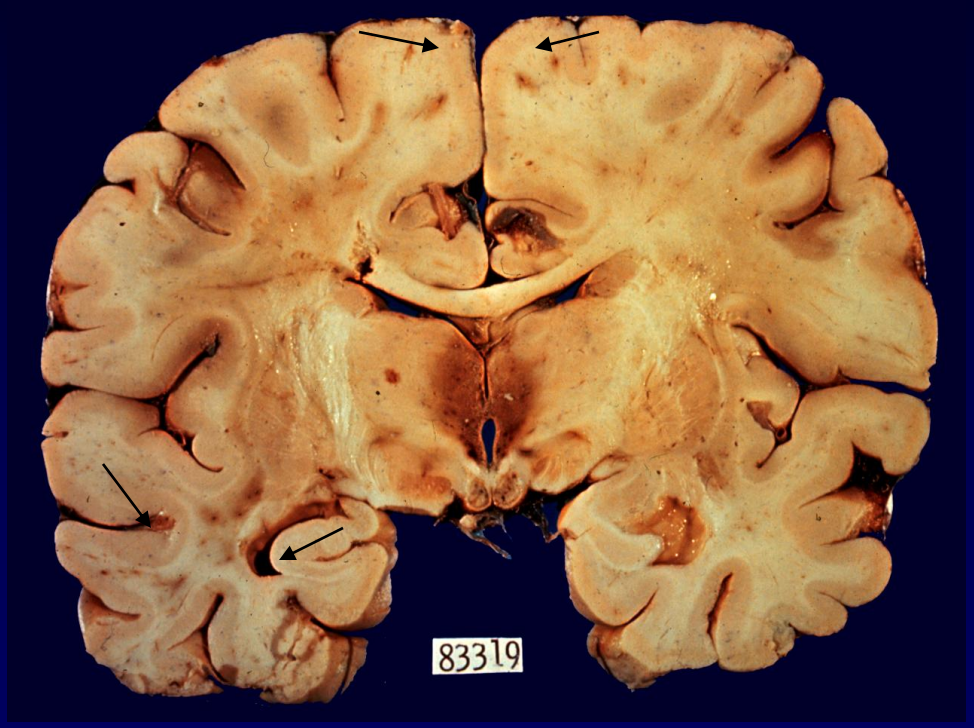
- Cellular and molecular mechanisms
- Genetic susceptibility and epigenetic modifiers
- Animal models: pathophysiology, dysmorphology, brain imaging, prevention, intervention
- Epidemiology: drinking pattern, prevalence
- Diagnosis: in utero ultrasound, 3D-facial imaging, brain imaging, cognitive and behavioral phenotype
- Prevention: Brief interventions pregnancy, nutrition, nutritional supplements (choline)
- Intervention: Cognitive, pharmacologic, policy

Brain Lesions in Alcoholics

- Alcohol Neurotoxicity
- Wernicke's encephalopathy: N,EN
- Hepatocerebral degeneration: L,EN
- Trauma: EI
- Fetal Alcohol Syndrome: EN, N
- Central Pontine Myelinolysis: N, EN, G
- Marchiafava-Bignami Syndrome: N, EN, G

N - nutritional; EN - ethanol neurotoxicity;
EI - ethanol intoxication
L - liver-brain toxcity; G - glial toxicity

Wernicke's Encephalopathy



Prevalence 0.8-2.8% of consecutive autopsies

- Alcohol replaces nutritive calories and causes nutrient malabsorption
- Brain lesions due to thiamine deficiency are potentiated by alcohol neurotoxicity
- Severe neurological impairment, including memory loss, oculomotor dysfunction, and gait ataxia

Concerns Regarding a Merger of NIAAA and NIDA

- Institute priorities drive funding, and funding drives science.
- An institute on addictions will prioritize research on addiction.
- The enormous public health burden from the non-addictive use of alcohol will not be adequately addressed, and research on the health benefits of alcohol will be orphaned.
- We will lose the highly integrated, systems approach of NIAAA that is necessary to understand the effects of alcohol use, abuse, and dependence at the molecular, genetic, cellular, organ, medical, psychological, social, and policy levels.

Concerns over Merger

There are no barriers to collaboration on addiction research that require a merger between NIDA and NIAAA.

There are no apparent scientific benefits to merger that could outweigh the enormous potential disadvantages.