National Institute on Alcohol Abuse and Alcoholism

Alcohol Use Disorders and Seizure/Epilepsy

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ICARE

March 24, 2014

National Institute on Alcohol Abuse and Alcoholism

NIAAA Workshop

Alcohol Consumption, Seizure and Epilepsy: Molecular, Cellular & Neural Circuit Mechanisms

RSA Satellite Meeting
Division of Neuroscience and Behavior, NIAAA, NIH

Saturday June 22, 2013

8:30 am – 4:30 pm

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NIAAA Workshop - Speakers

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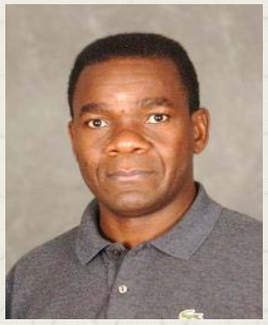
Glia in Seizure & Epileptogensis




$GABA_AR$ Subunit Plasticity

NIAAA Workshop - Agenda

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Morning

8:40 – 8:50 **Dr. Qi-Ying Liu** Introduction

8:50 – 9:35 **Dr. Helen E. Scharfman** The Neurobiology of Seizure and Epilepsy

9:35 – 10:15 **Dr. David M. Lovinger** Synaptic Substrates of Alcohol Use- and Withdrawal-Induced Seizure andEpilepsy

10:30 – 11:15 **Dr. Kari J. Buck** Genes & Neural Networks Underlying Seizure Susceptibility and Alcohol Withdrawal Seizure

11:15 – 11:55 **Dr. Daniel D. Savage** Prenatal Alcohol Exposure and Seizure/Epilepsy Susceptibility

Afternoon

1:00 – 1:40 **Dr. Prosper N'Gouemo** Ion Channels and Alcohol-Related Seizure and Epileptogenesis

1:40 – 2:20 **Dr. Sally McIver** Glia in Seizure and Epileptogenesis

2:35 – 3:15 **Dr. Richard W. Olsen** $GABA_A$ Receptor Subunit Plasticity in Alcohol Use- and Withdrawal-Induced Seizure/Epilepsy

3:15– 3:55 **Dr. A. Leslie Morrow** Molecular Mechanisms of Alcohol Withdrawal-Induced CNS Hyperexcitability: the Role of Neuromodulatory Systems

3:55 – 4:30 **Discussion and Summary**

Alcohol Affects Virtually all Neurotransmission Systems

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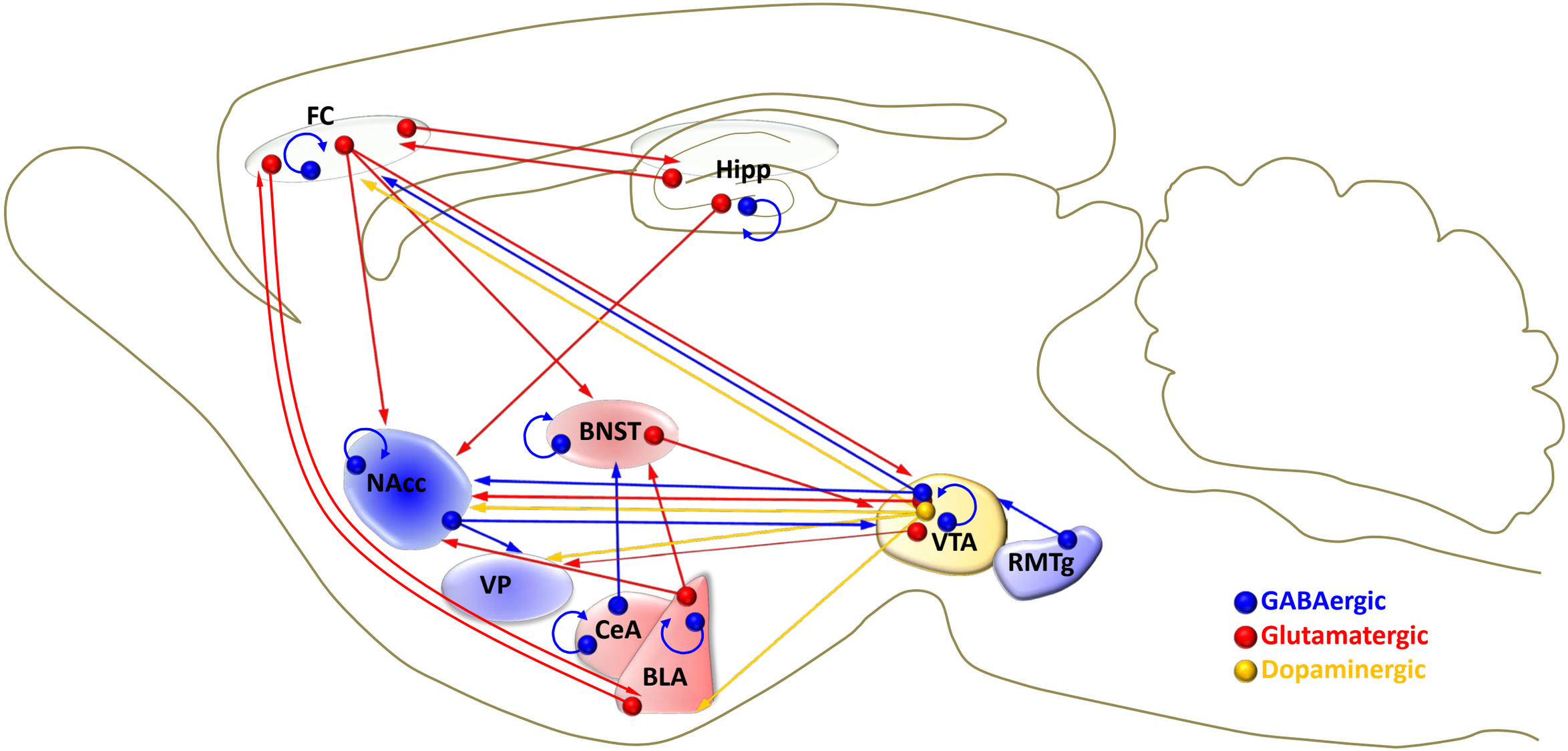

Concentration-Dependence of Alcohol Effects

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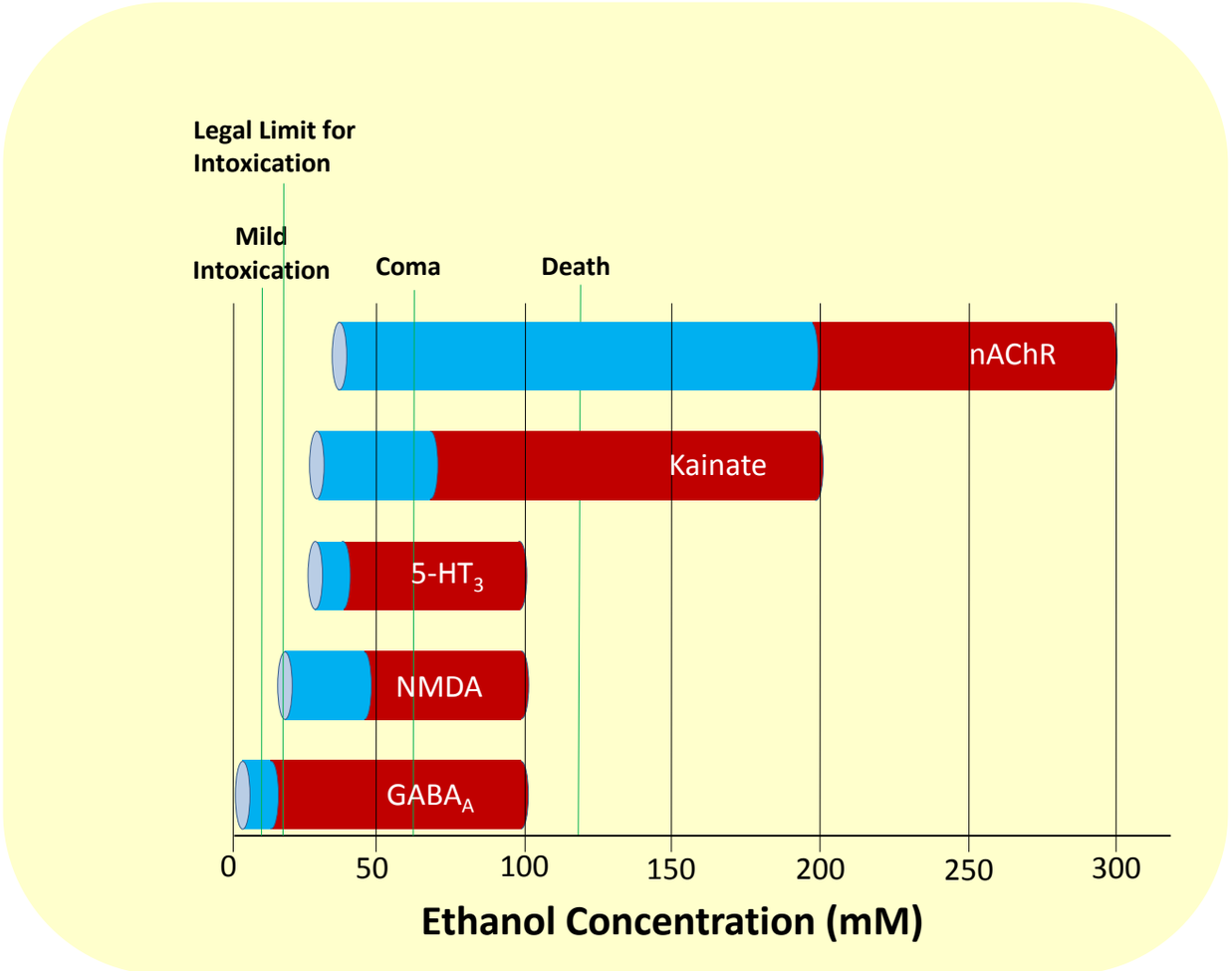

(Modified from Krystal *et al.*, 2006)

Alcohol and GABAergic Synapse

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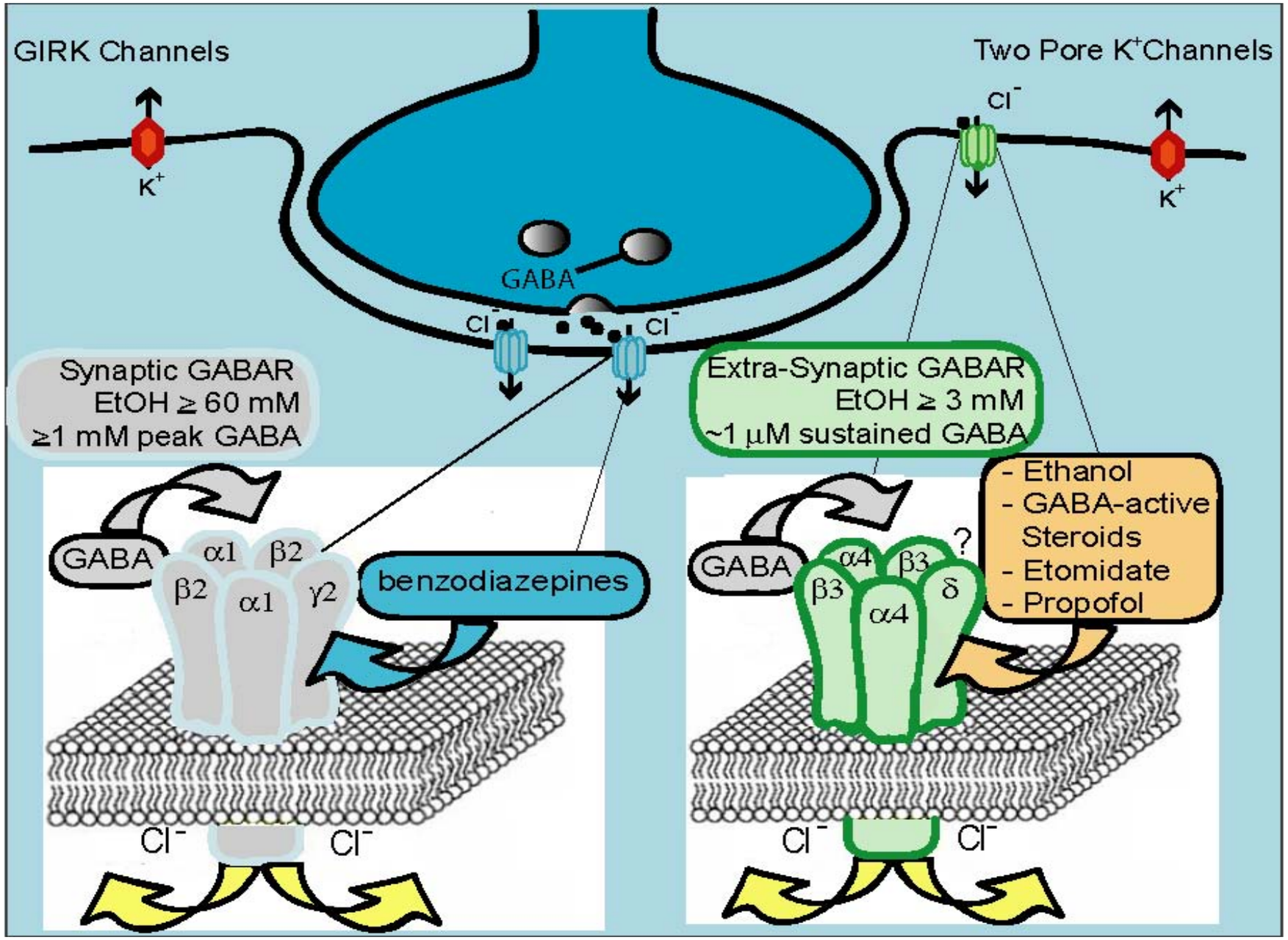

Wallner et al., PNAS (2003)

Alcohol and GABAergic Synapse

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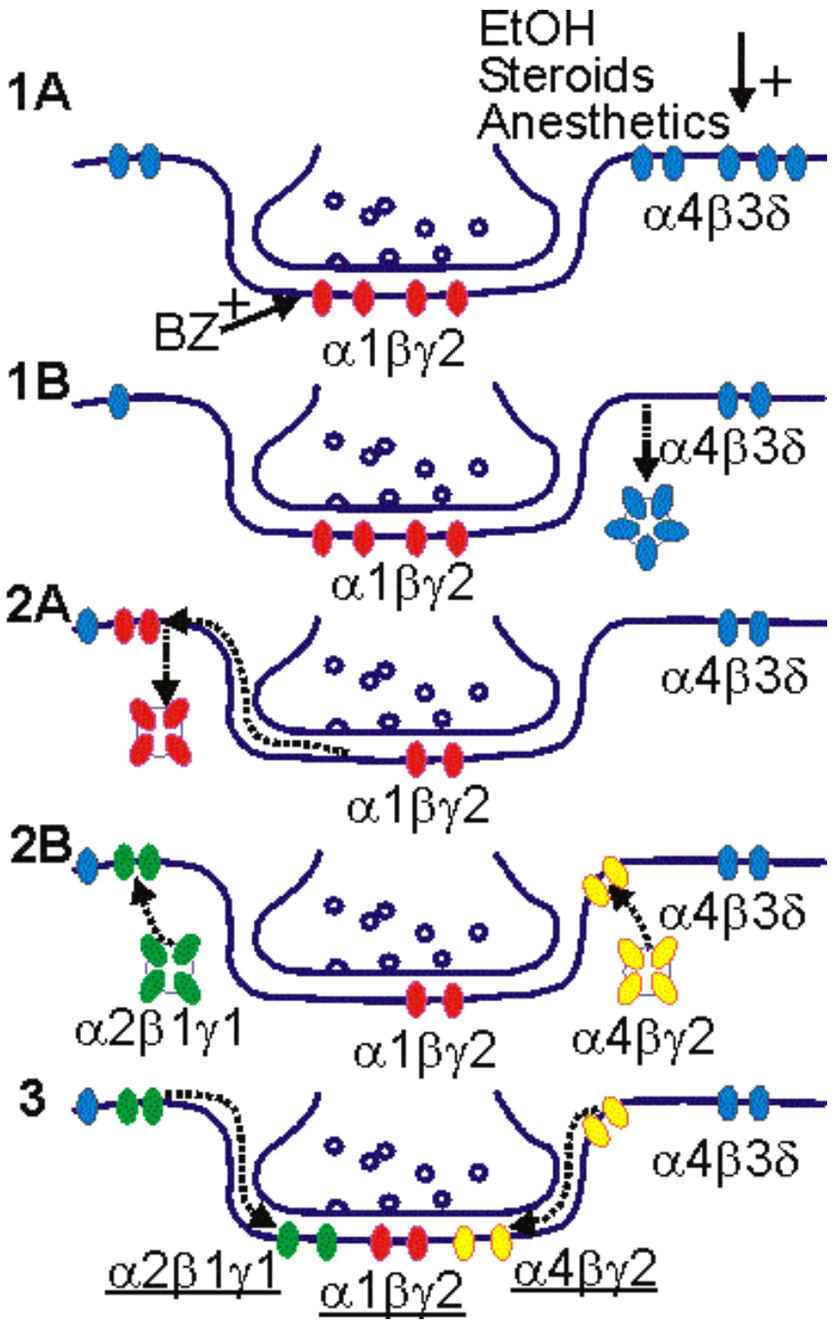

1A. Binding of positive modulators to $GABA_A$Rs overstimulation.

1B. Within 1hr, internalization of δ-containing $GABA_A$Rs that bind to positive modulators (e.g., EtOH, α4βδ), leading to reduced tonic inhibition, hyperexcitability, acute tolerance.

2A. Within a few hrs, internalization of synaptic $GABA_A$Rs (e.g., α1βγ2), leading to reduced synaptic inhibition, hyper-excitability, cross-tolerance to BZs.

2B. At the same time, increased bio-synthesis of α4 and γ2, as well as α2, β1, and γ1; assembly; trafficking to surface membrane.

3. Major increase in surface α4βγ2, including some synaptic localization, and α2β1γ1 (synaptic). Altered kinetics and pharmacology of mIPSCs, including EtOH sensitivity (due to α2β1γ1 and/or α4βγ2).

Neurosteroids and Risk for Alcoholism

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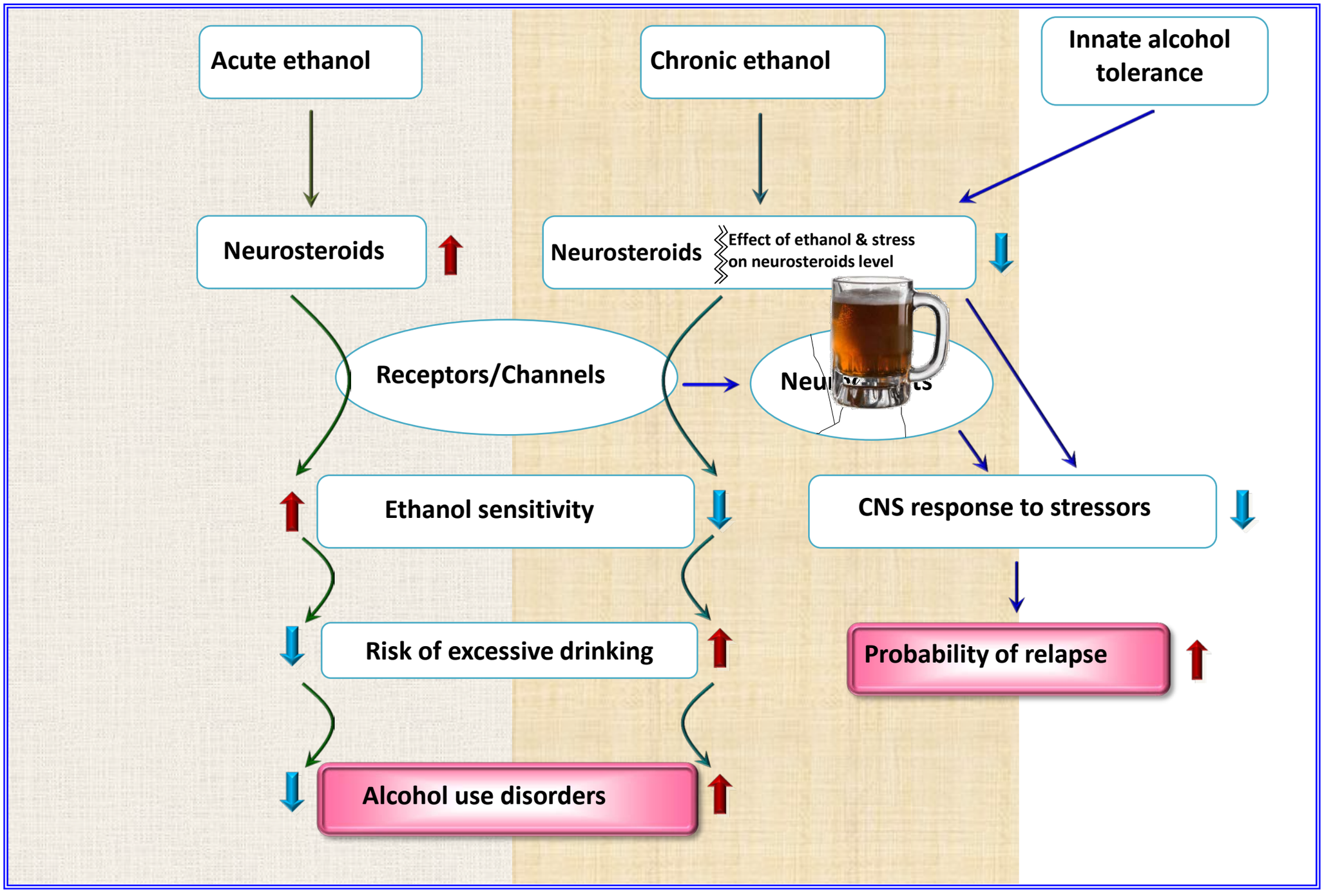

Inhibitory/Excitatory Balancing and Imbalance

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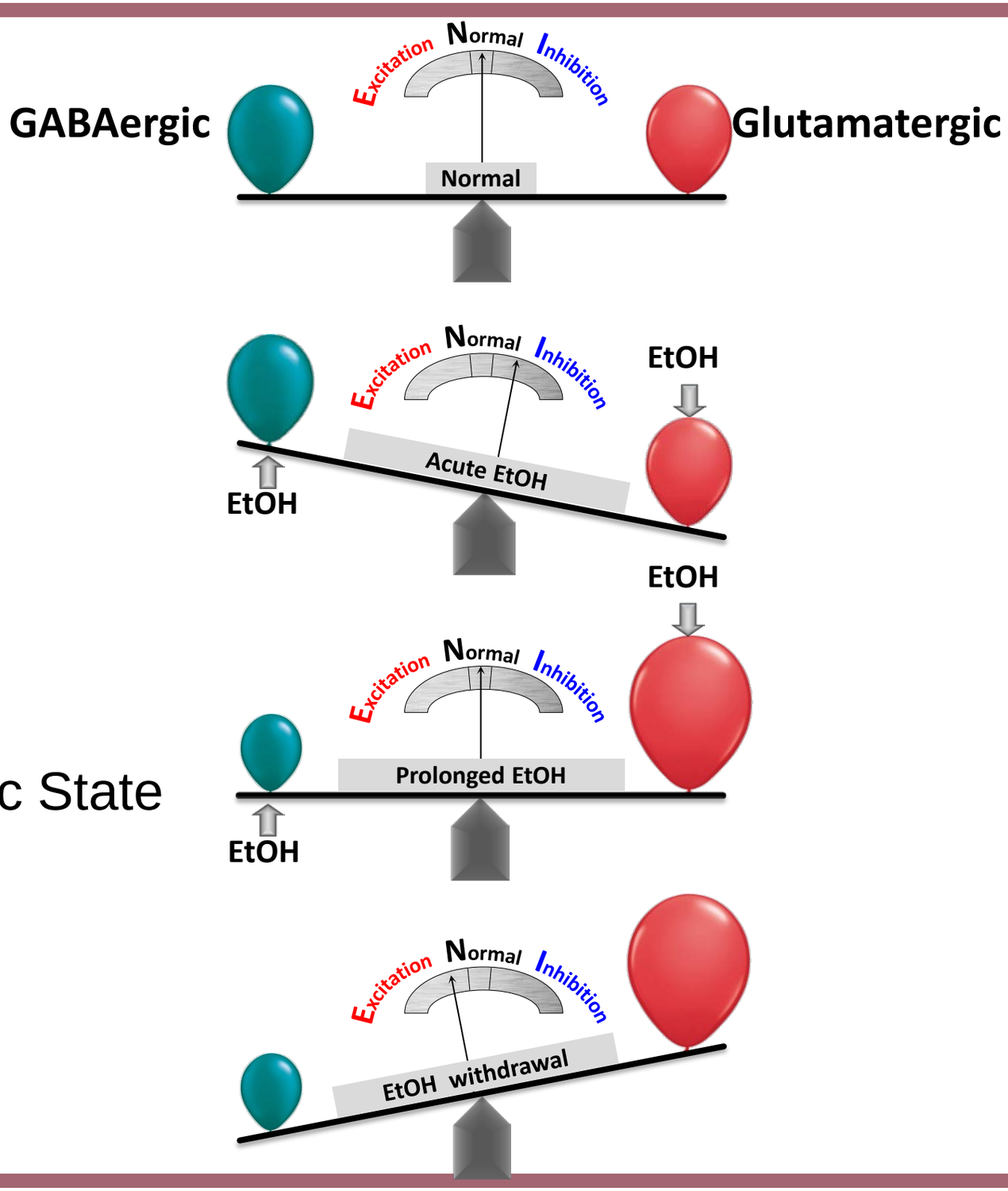

Allostatic State

Persistent Decrease in Seizure Threshold in CIE Rats after Cessation of Ethanol Treatment

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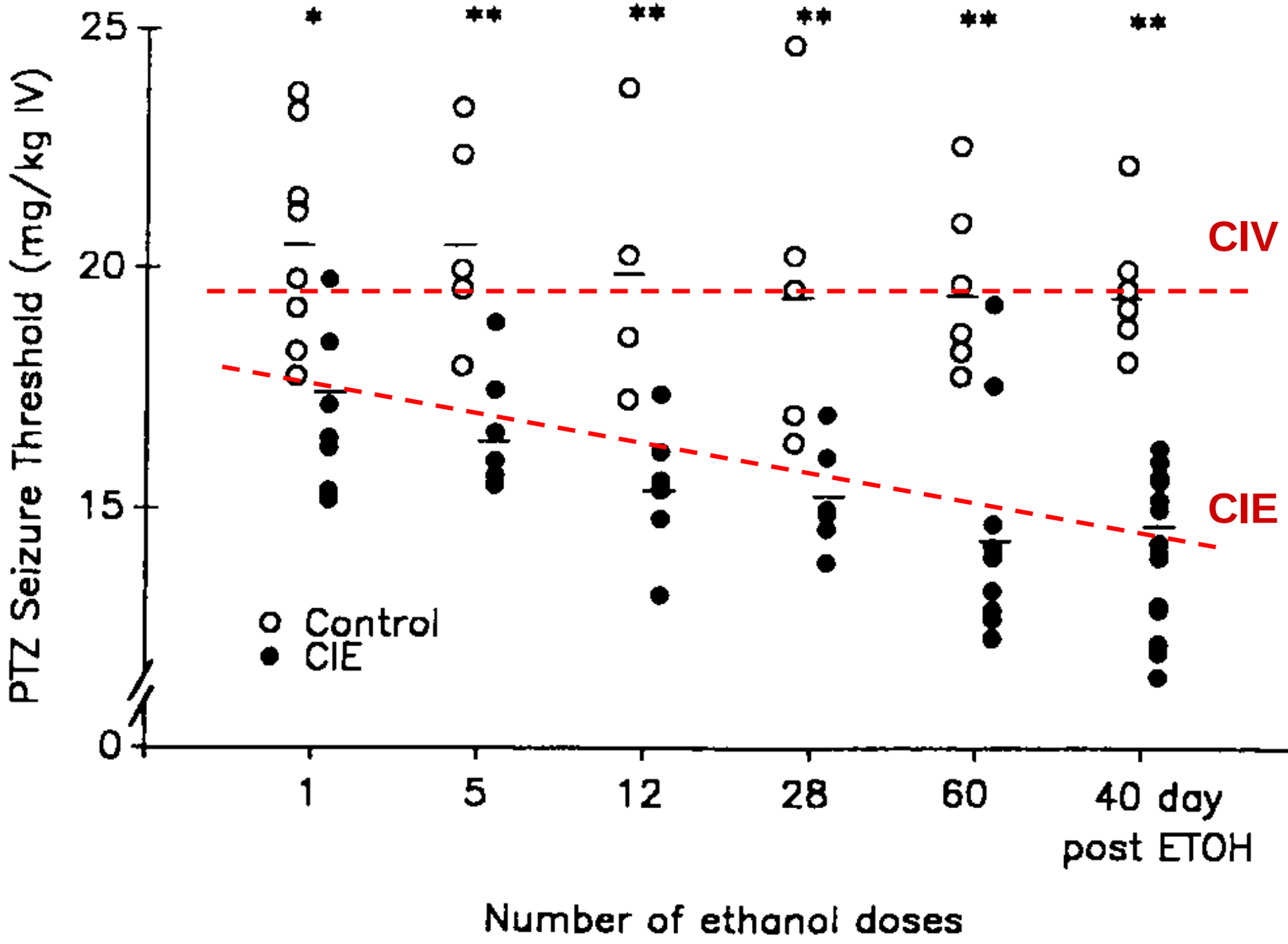

Kokka, N. et al., A.C.E.R. 17: 525-531, 1993

Alcohol Withdrawal Seizures

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- Partial seizures
- Generalized tonic-clonic seizures
- Status epilepticus

There are still significant gaps in the mechanisms underlying neuronal hyperexcitability that leads to alcohol withdrawal seizures.

Cellular Mechanisms of Seizure Generation

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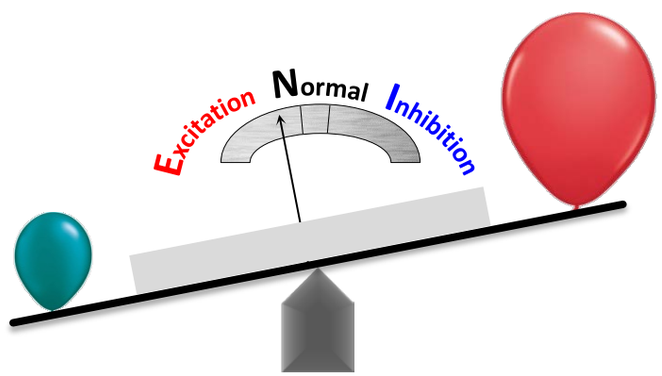
- Excitation (too much)
  - Ionic—inward Na^{+}, Ca^{++} currents
  - Neurotransmitter—glutamate,
- Inhibition (too little)
  - Ionic—inward Cl^{-}, outward K^{+} c
  - Neurotransmitter—GABA



Inhibitory/Excitatory Imbalance as a Cause of Epilepsy

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- Reduced numbers of GABAergic interneurons
- Increased recurrent excitatory circuitry
- Many other changes in GABA and glutamate Neurotransmission
- Gliosis
- Angiogenesis
- Proliferation of neurons that are abnormal

Three Stage Hypothesis for Acquired Epilepsy

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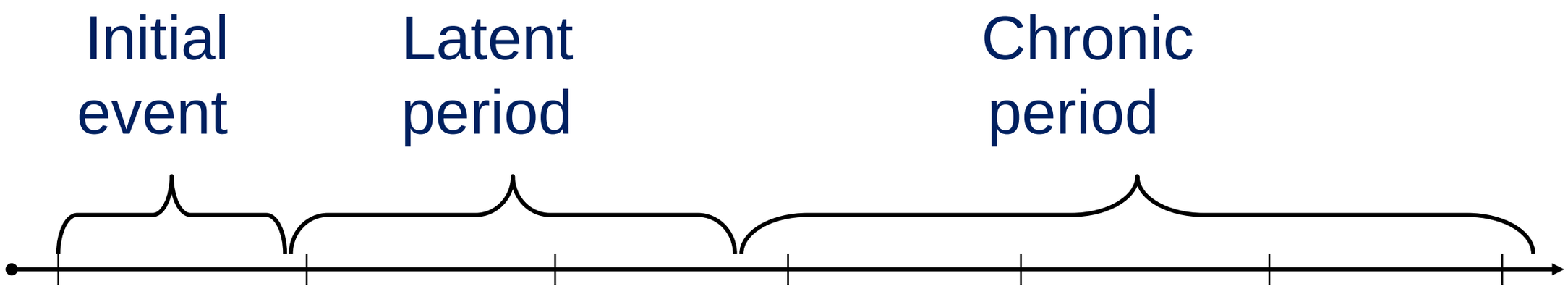

Scharfman, Pedley (2006): The Neurobiology of Disease

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Does prenatal ethanol exposure increase:

- Risk of developing epilepsy ?

or

- Enhance seizure susceptibility ?

Prenatal Ethanol Exposure & Risk of Epilepsy

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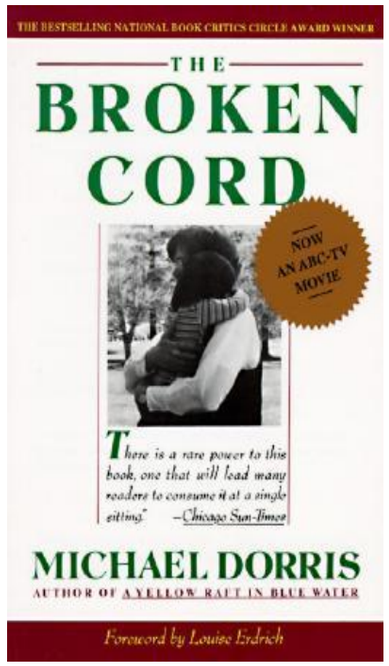
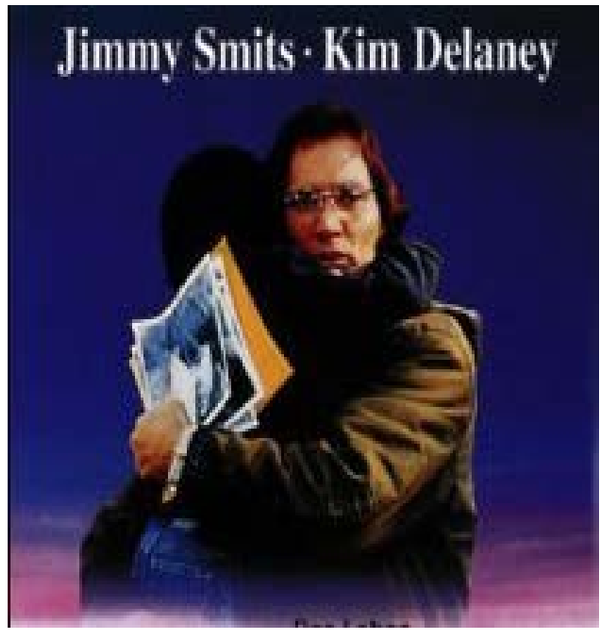
Prevalence in general population (all ages) <1%
(higher in young children and elderly patients)

Prevalence in FAS or prenatal ethanol-exposed children:

Olegaard et al., 1979	**10%**
Iosub et al., 1981	**3%**
Majewski & Goecke, 1982	**12%**
Spohr & Steinhausen, 1987	**10%**
O'Malley & Barr, 1998	**21%**

Impression:
"*Seizures are often found in children with FAS*"





Prenatal Ethanol Exposure & Risk of Epilepsy

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Early studies consisted mainly of case reports or small numbers of individuals, frequently the most severely affected patients

Abel, 1998	**(Meta-analysis of 550 subjects)**	**3%**
Bell et al., 2010	**(Canadian Study – 425 subjects)**	**5.9%**
Sun et al., 2009	**(Danish Cohort – 80,526 subjects)**	**1.8 fold ↑**

BUT, the perception among pediatric neurologists and clinical psychologists: “Epilepsy is not that common among patients with FASD”

Summary - Clinical Studies

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- **Most severely affected children with FASD at greater risk of epilepsy**

- **Link between fetal EtOH exposure & epilepsy may be EtOH dose-dependent**
  - **No evidence suggesting low to moderate drinking linked to epilepsy**
  - **Higher levels of consumption may lead to:**
    Neonatal withdrawal seizures, Febrile Seizures
    Seizure episodes and / or Epilepsy

- **No clear indication of whether prenatal ethanol exposure is associated with specific seizure types.**

Summary - Preclinical Studies

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- **Perinatal ethanol exposure may differentially affect seizure susceptibility in different animal models of epilepsy**
- **Interpretation of preclinical data across studies using similar models of epilepsy difficult, primarily due to:**
  - **Variations in perinatal ethanol exposure paradigms (species, ethanol dose, timing of exposure)**
  - **But also prospect of experimental confounds (malnutrition, maternal stress).**
- **More moderate ethanol exposure does not appear to increase seizure susceptibility and may lower susceptibility in some cases.**
- **Higher ethanol doses, delivered during critical periods of greatest neural susceptibility to ethanol's cytotoxic effects appear more likely to lower seizure threshold**
- **Lack of systematic follow-up of initial observations to determine mechanisms underlying altered seizure susceptibility**

Alcohol and Seizure/Epilepsy

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- Alcohol use disorders (AUD) and epilepsy affect large numbers of Americans.
  - AUD affects 18 million and costs an estimated $185 billion/year
  - Epilepsy affects ~ 3 million Americans.
- Chronic alcohol exposure induces complex adaptive changes in the CNS, allowing the brain to function in an allostatic state in the presence of alcohol.
- Alcohol withdrawal reveals the hyper-excitable state and causes symptoms, including severe and life-threatening seizures, that often make quitting drinking difficult.
- Alcohol abuse and withdrawal may decrease seizure threshold and increase frequency/severity of seizure in epilepsy patients (moderate and occasional drinking might be okay).
- Meta-analysis found an association between alcohol consumption and epilepsy/unprovoked seizures.

Alcohol and Seizure/Epilepsy (continued)

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- High prevalence of epilepsy and seizure in patients with fetal alcohol spectrum disorders.
- Risk factors:
  - Genetic susceptibility
  - Metabolic perturbations
  - Cumulative effects and possible multiple organ damage including brain
  - High total alcohol consumption, including binge drinking
  - Repeated severe intoxication and withdrawal.

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Thank You