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Effects of alcohol on children

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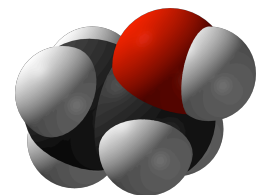
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Ethanol: evolution, medicine, culture

- A straight-chain alcohol, colorless and volatile
- Produced by yeast and intoxicates those who try to eat its food
- Consumption embedded in human culture that itself bears traces of intoxication
 - some would say this of all our civilization
- Ethanol is a pharmacologically active substance
- Early medical application broad but now limited interest in its pharmacodynamic action
- Solvent (second most common after water) or preservative
- Used as an excipient in more than 700 liquid preparations that may be administered to neonates, infants and children



Children meet alcohol

- Prenatal, consumption by mother
- Prenatal, epigenetic effects of father's consumption
(Finegersh *et al.*, *Alcohol* 2015; 49, 461-479)
- During breastfeeding
- Accidental consumption
- Medical procedures
- Excipients
- Experimentation and eventual regular consumption
- In addition to direct pharmacological effects the effects mediated by changes in lifestyle

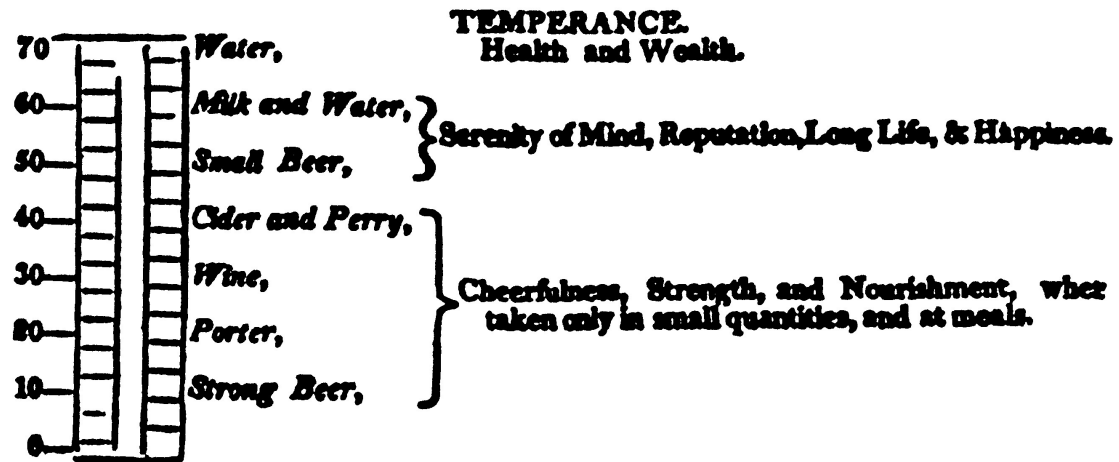
Pharmacodynamics: introduction

- excitation
(sometimes of neuronal inhibition)

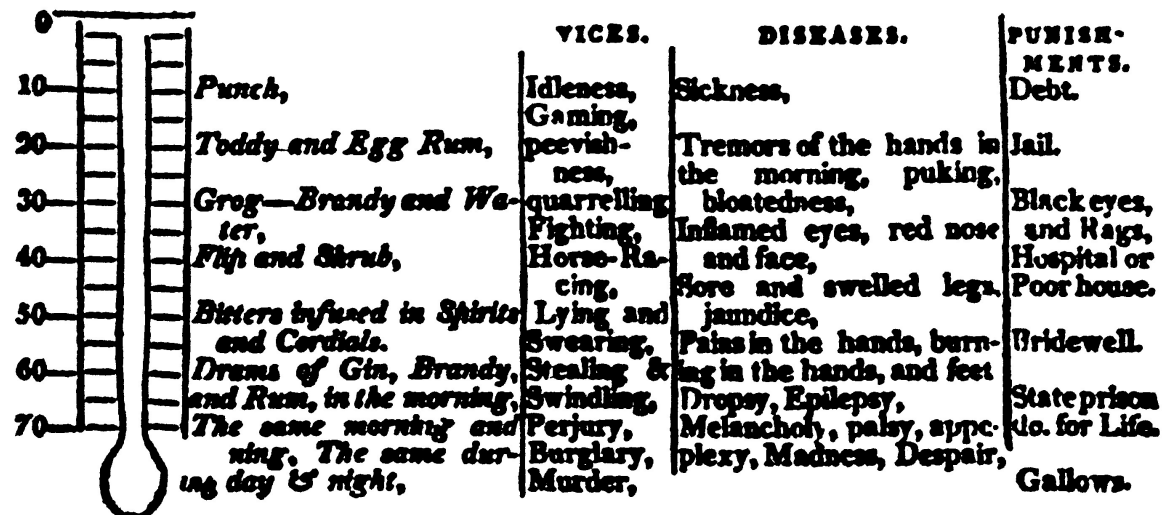
- inhibition
(sometimes of neuronal excitation)

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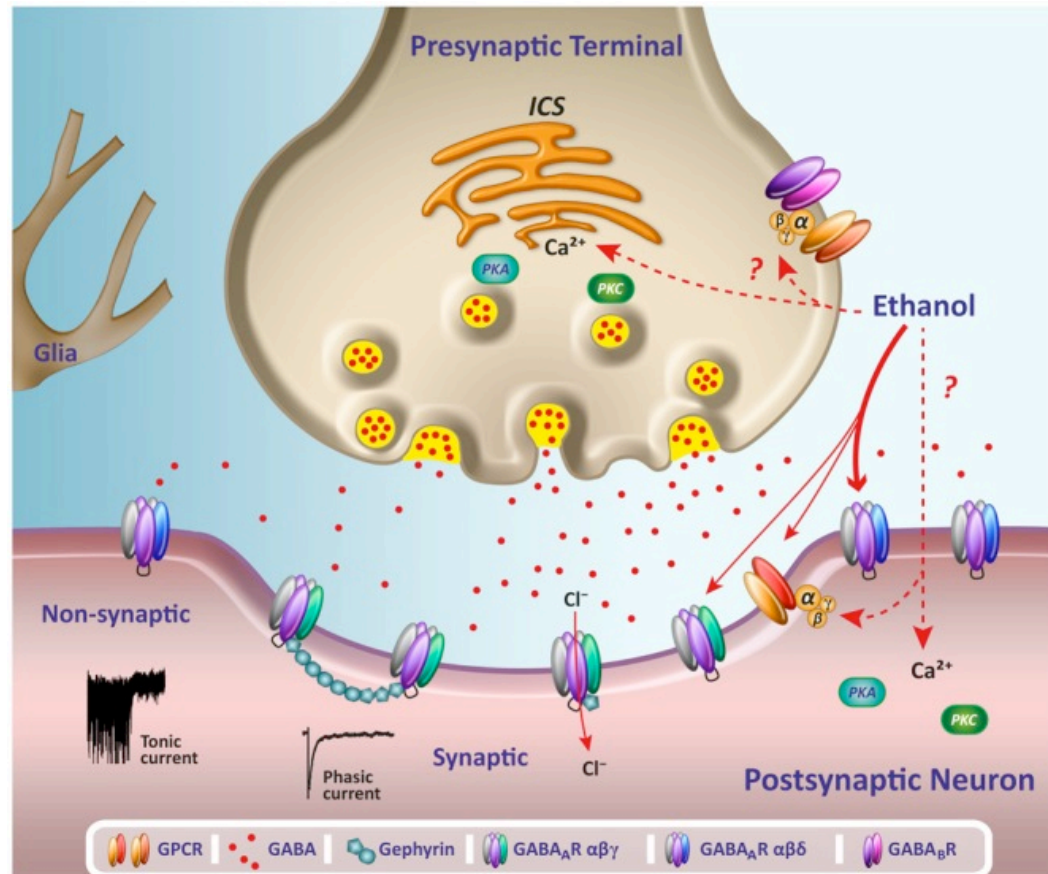
A MORAL AND PHYSICAL THERMOMETER. *A scale of the progress of Temperance and Intemperance.—Liquors with effects in their usual order.*



INTEMPERANCE.



GABA: the variety of actions of ethanol

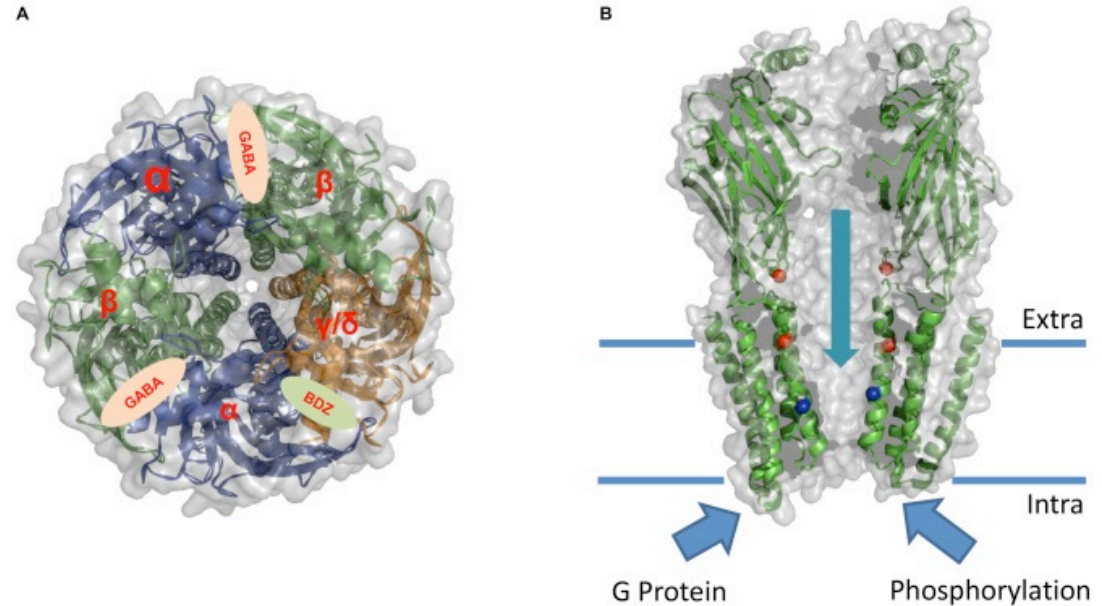


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6

Förstera et al., *Frontiers in Cellular Neuroscience* 2016; 10, 114

Sites of action for allosteric modulation of GABA_A receptors



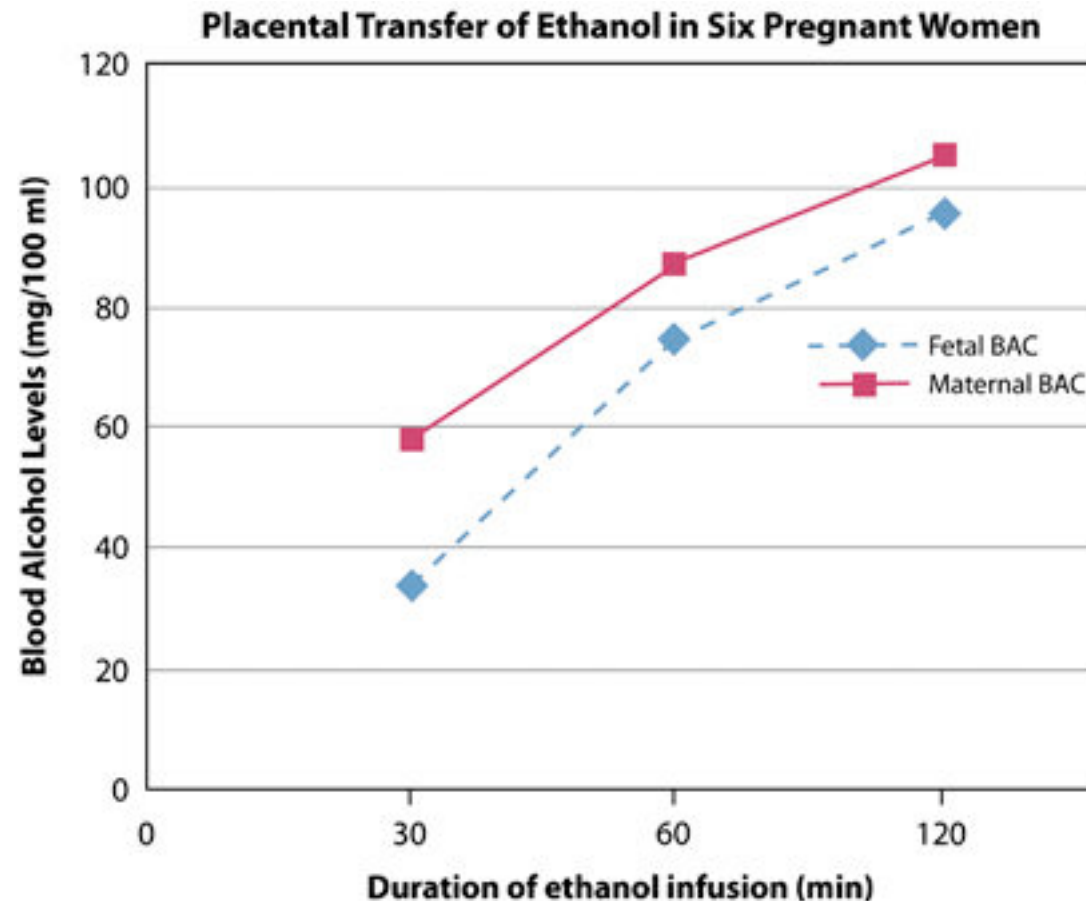
- A: upper view; putative subunit stoichiometry and global architecture of the $\alpha\beta\gamma/\delta$ GABA_AR, showing the binding sites for GABA and benzodiazepines
- B: lateral view; suggested binding sites for ethanol (red) and picrotoxin (blue)

Fetal alcohol spectrum disorders

- Early mortality; abnormal appearance; perception impaired
- Wide range of CNS abnormalities
 - Neural tube, corpus callosum, cerebellum
 - Reduction of number of stem cells
 - Increased neuronal proliferation and migration
 - Delay in neuronal differentiation
- Neurodevelopmental impairments
 - In almost any domain of CNS function

Ethanol in the mother and child

- In the USA 12.5% of pregnant women reported some alcohol use, and 1.6% frequent use (2001)
- FASD prevalence estimates range from 0.2 to 50 per 1000 live births
- U.S. estimated FAS annual incidence 8,000-28,000
- Alcohol detectable in fetus 1 min after maternal ingestion but concentration raises more slowly

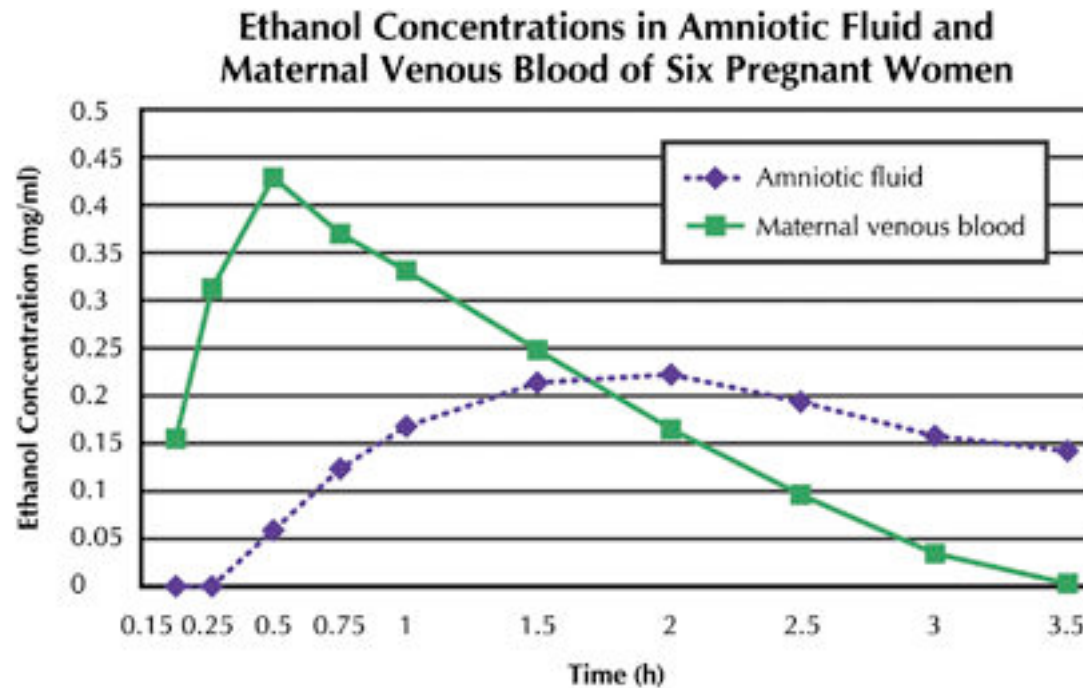
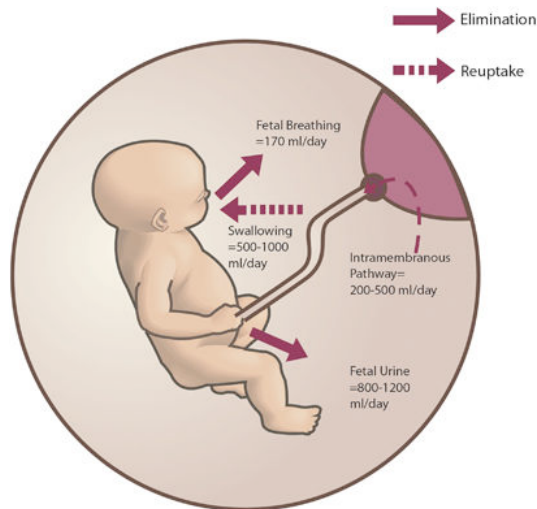


FASD Variabilities

- Metabolic elimination in pregnant women varies eightfold (from 0.0025 to 0.02 g dl⁻¹ h⁻¹)
- At birth physiological changes alter the neonate's metabolic capacity and it rapidly rises to a mean value of 83.5% of the mother's capacity
- FASDs are highly recurrent and younger siblings have increased risk
- Mothers of children with FAS have been found to drink faster, get drunk quicker and to have higher BACs
- A modest increase in the prevalence of a polymorphism of alcohol dehydrogenase, which increases susceptibility to adverse outcomes from PAE has been reported

Ethanol in maternal blood and in amniotic fluid

- Pathways of amniotic fluid recirculation.²⁷ Production and reuptake are usually near equilibrium and therefore alcohol elimination through these pathways is highly ineffective.

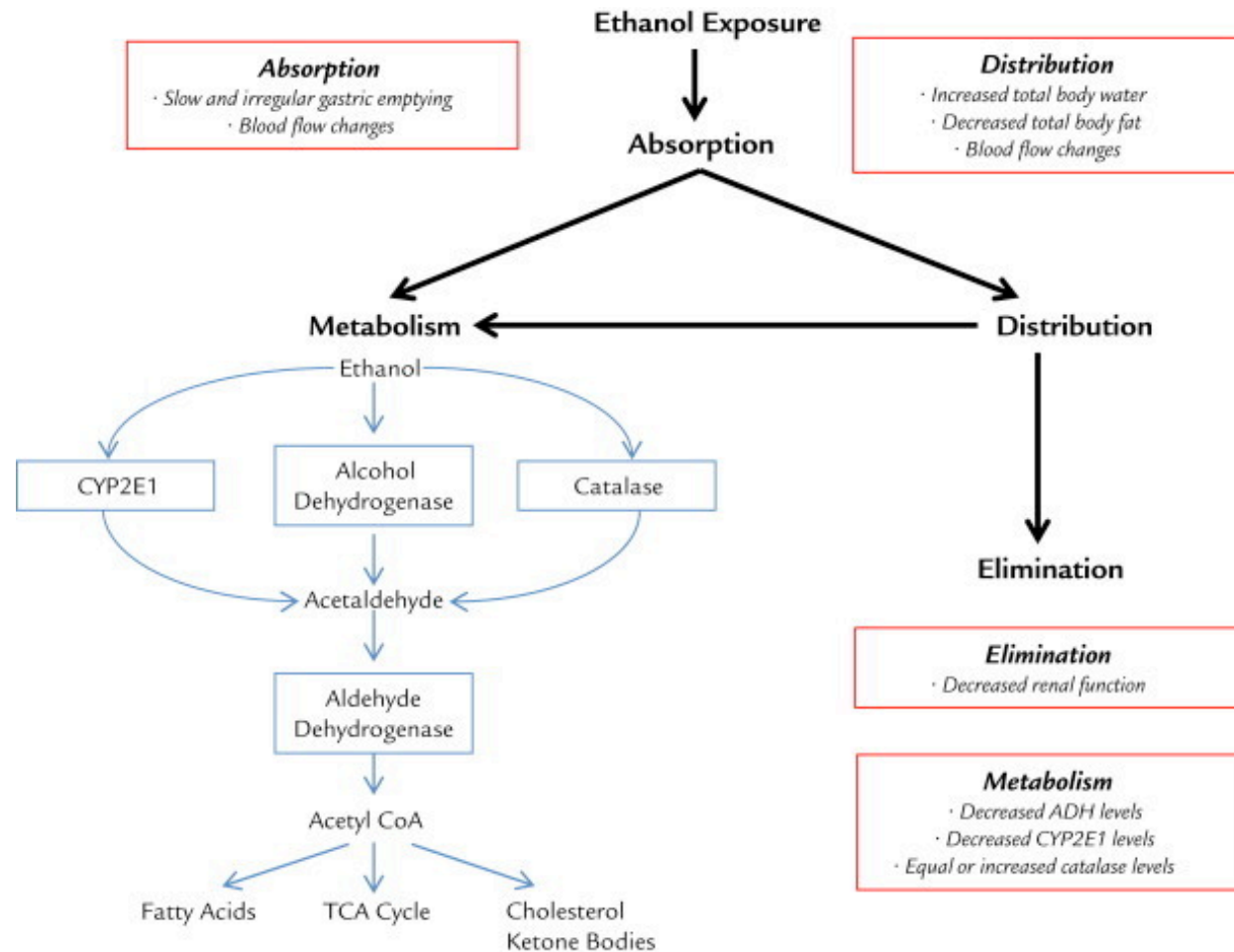


Pharmacokinetics

- Absorbed rapidly in the stomach and intestines, largely in duodenum
 - gastric emptying rate important
- Distribution freely in water
 - water content important (larger in males and younger people)
- Metabolized (more than 90%) to acetaldehyde mostly by alcohol dehydrogenase (mainly Class I), subsequently oxidized to acetate by acetaldehyde dehydrogenase
- In children (<5) alcohol dehydrogenase is immature but other, microsomal enzymes operate; oxidation by catalase is possibly unimportant in vivo

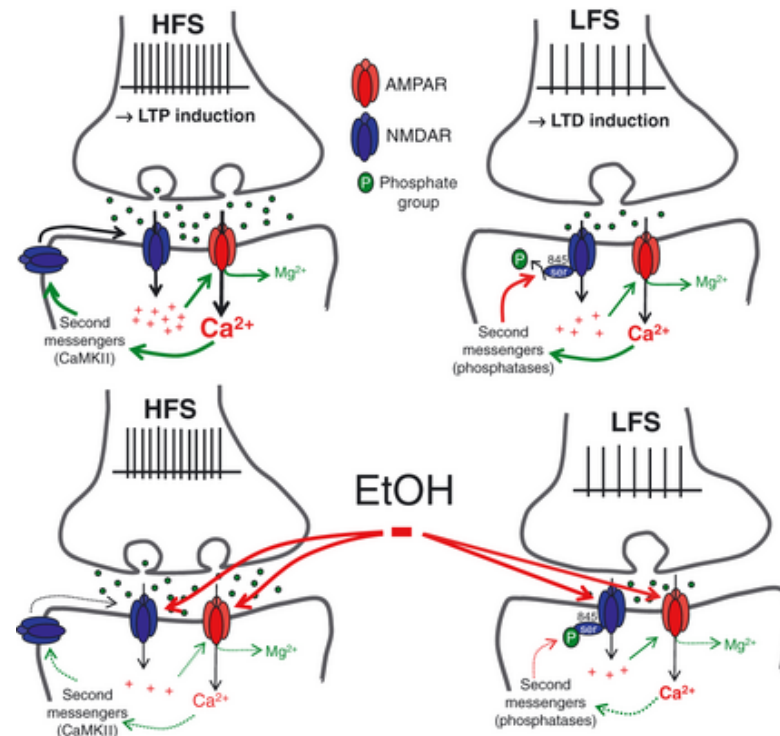
Ethanol pharmacokinetics and neonatal factors

- Red boxes show where infants differ from adults



Acute effect of ethanol on glutamate receptors

- Ethanol can non-competitively inhibit glutamate receptors at clinically relevant concentrations
- NMDA receptors are more sensitive (25 mM; about 1.1 ‰ BAC)
- Kainate and AMPA receptors in some conditions sensitive
- Inhibition mostly in hippocampus, amygdala and striatum
- May be part of foetal alcohol syndrome

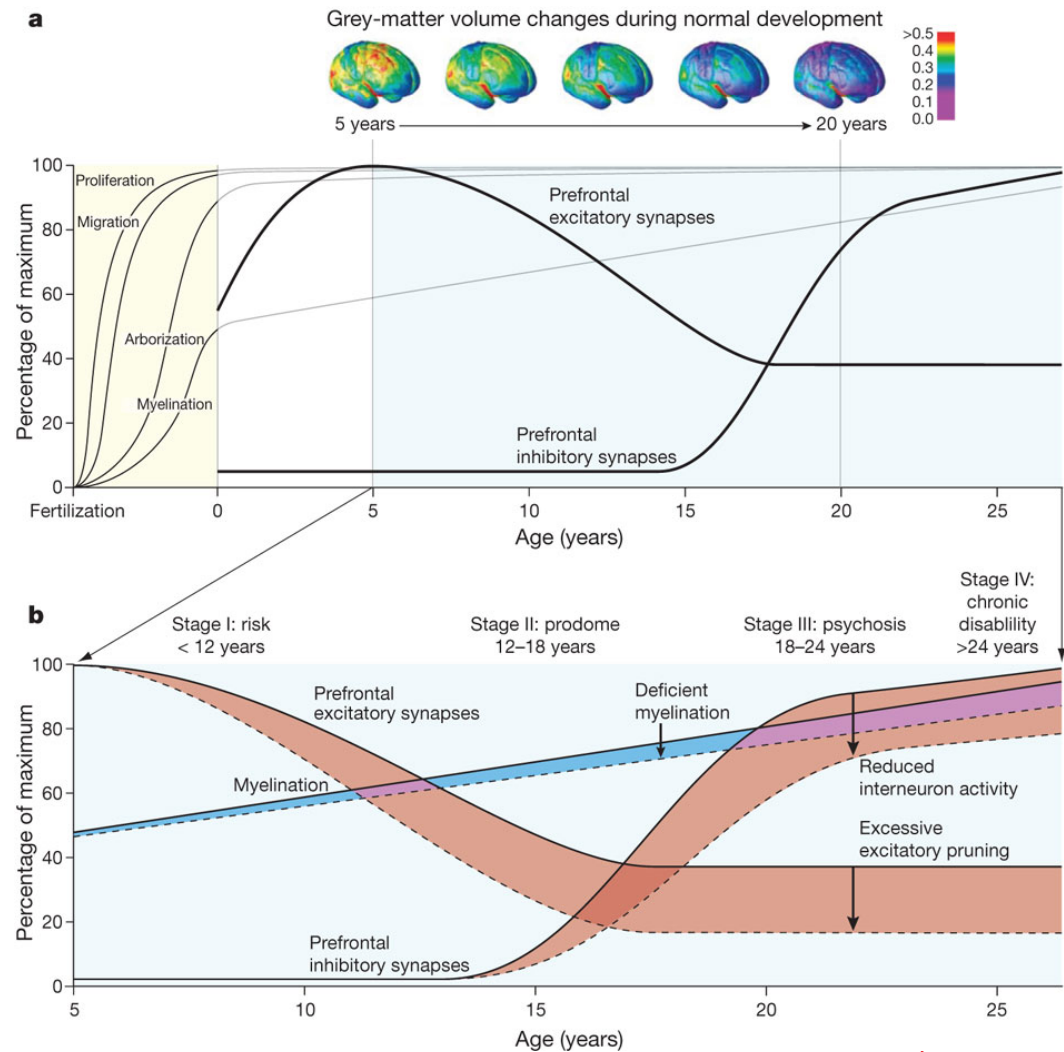


The developing brain

- proliferation and migration of neurons almost complete at birth
- arborization near complete, myelination proceeds until 5
- prefrontal excitatory system in dynamic development until 18, inhibitory – until 30

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TR Insel *Nature* **468**, 187-193 (2010) doi:10.1038/nature09552

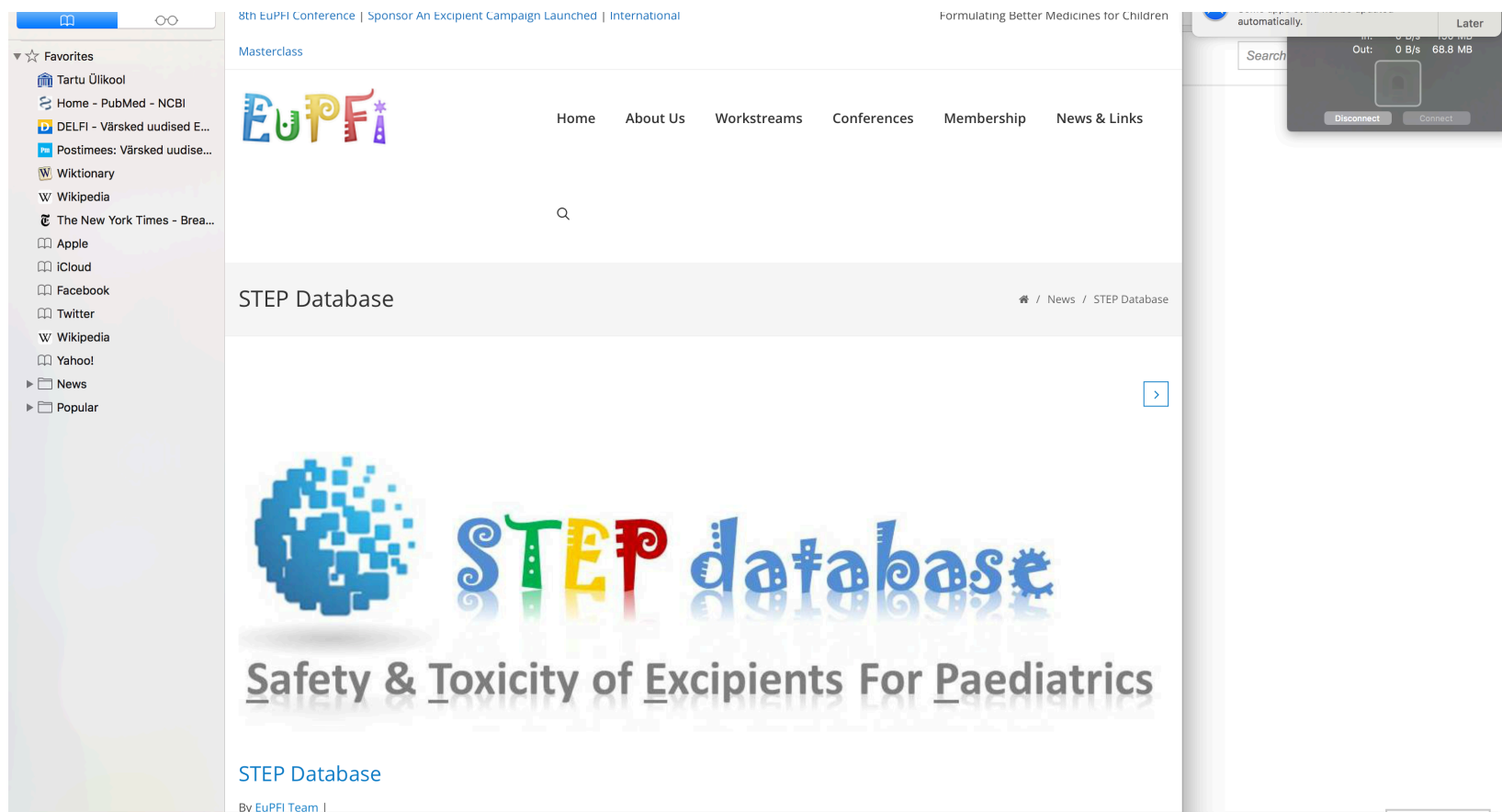


nature

We do probably know ... not enough

- Used as an excipient in more than 700 liquid preparations that may be administered to neonates, infants and children (Zuccotti & Fabiano, *Expert Opinion on Drug Safety* 2011; 10, 499-502)
- “Ethanol is present in more than 700 pharmaceutical preparations, ostensibly as an “inert” solvent or diluent” (*American Academy of Pediatrics Committee on Drugs, Pediatrics* 1984; 73, 405-407, citing Petroni & Cardoni, *Drug Therapy* 1978; 8, 72-93)
- Safety standards (FDA, AAPCD, EMA) now in place but scientific evidence meagre (Marek & Kraft, *Current Therapeutic Research: Clinical and Experimental* 2014; 76, 90-97)
- Important changes taking place (e.g., removal of ethanol from oral morphine solutions)

Excipient databases, including alcohol



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17

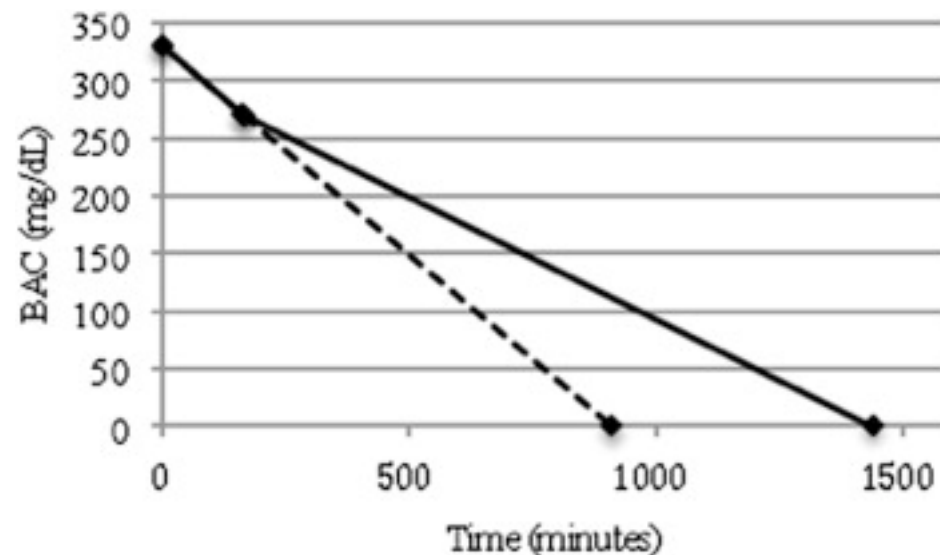
Salunke *et al.*, *International Journal of Pharmaceutics* 2013; 457, 310-322;
Salunke & Tuleu, *International Journal of Pharmaceutics* 2015; 492, 316-331

Alcohol intoxication in infants

- Rarely reported
- But more common than acknowledged
- Alcohol mixed into baby formula, given as sponge bath, umbilical cord dressing
- Blood levels measured <100 to >400 mg/dL
- Elimination rate mostly as in adults
- Acute alcohol well tolerated: recovery fast and no long-term consequences reported
- Case: 9-week old male, 9.5 kg; received baby formula with appr. 90 ml of vodka, HR=160, respiration 22, temperature 97.7F; BAC 330 mg/dL; dazed at admission but happy in 1 h

Case Report: Alcohol elimination over time

- BAC data limited to 2 + 1 points
- extrapolated 21.6 mg/dL/h
- this would be close to older children and adults
- very high rate has been reported but also data limitations



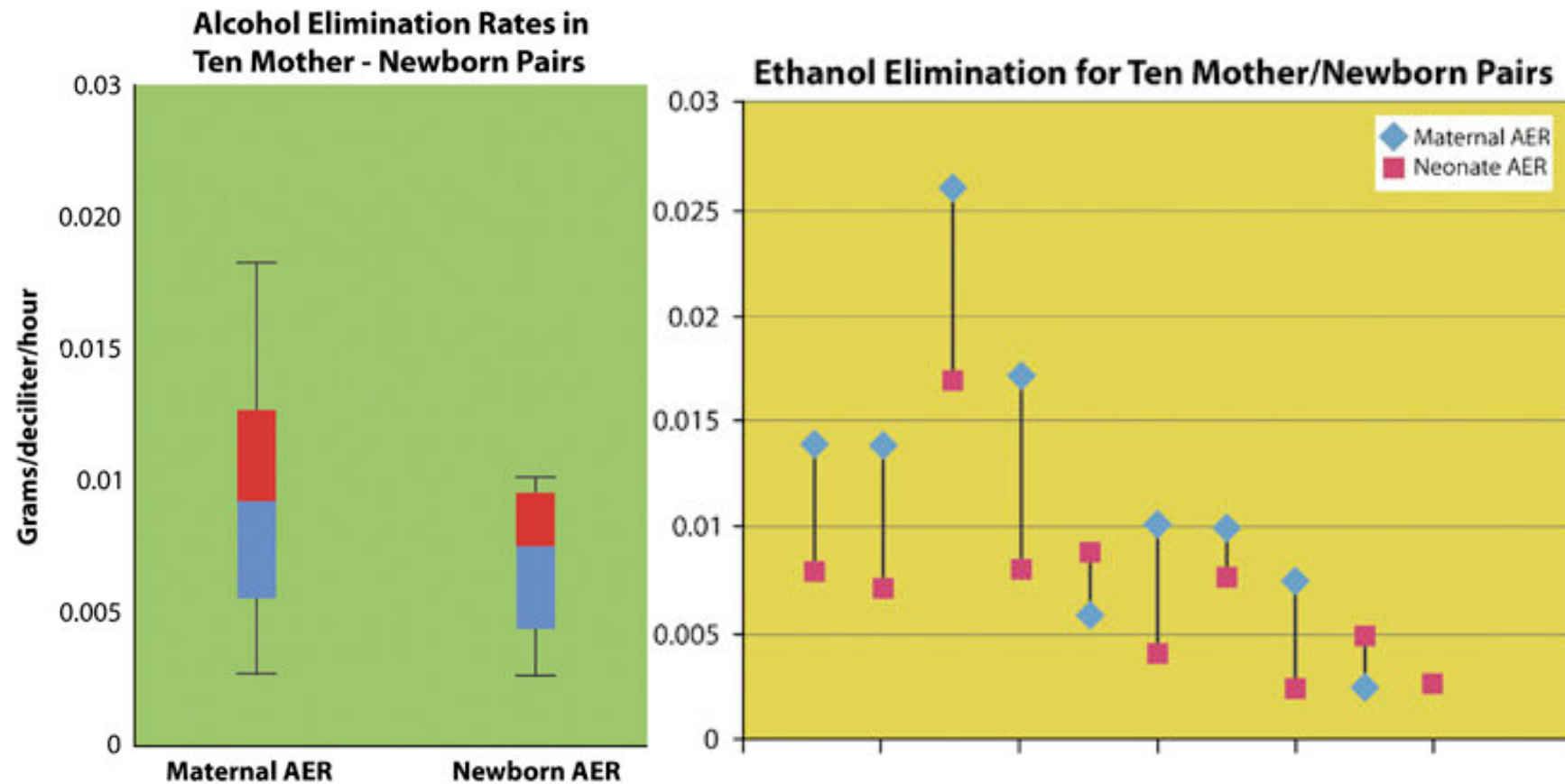
A few more cases

- IT: white wine mixed into 1-month old's formula; BAC 75 mg/dL, decrease in consciousness, tremor, fever; normal at 1 year (Palano *et al.*, *Minerva Pediatr* 2007; 59, 275-279)
- US: vodka in 7-month old's formula; BAC 183, tachycardia, mild hypotension (Chikwava *et al.*, *Pediatr Dev Pathol* 2004; 7, 400-402)
- GB: 18-month old girl drank 200 ml of paracetamol elixir (10% ethanol); estimated BAC 187, Glasgow Coma Scale 3, hypotensive, recovered in 24 h (Tovey *et al.*, *J Accid Emerg Med* 1998; 15, 69-70)
- Three cases of intoxication by absorption, with largely similar outcomes

Alcohol intoxication in infants

- CDC records: one infant death due to alcohol intoxication between 1995 and 2007
- But in 2012 alone 1,349 ethanol exposures of children <5 years reported to the American Association of Poison Control Centres
- Seven cases were children younger than 18 months, one of these iatrogenic
 - recovery usually good, no abnormality at follow-ups
- Conclusively, intoxications are not rare but mostly occur at home and are not fatal

Mostly newborns have lower capacity to eliminate alcohol



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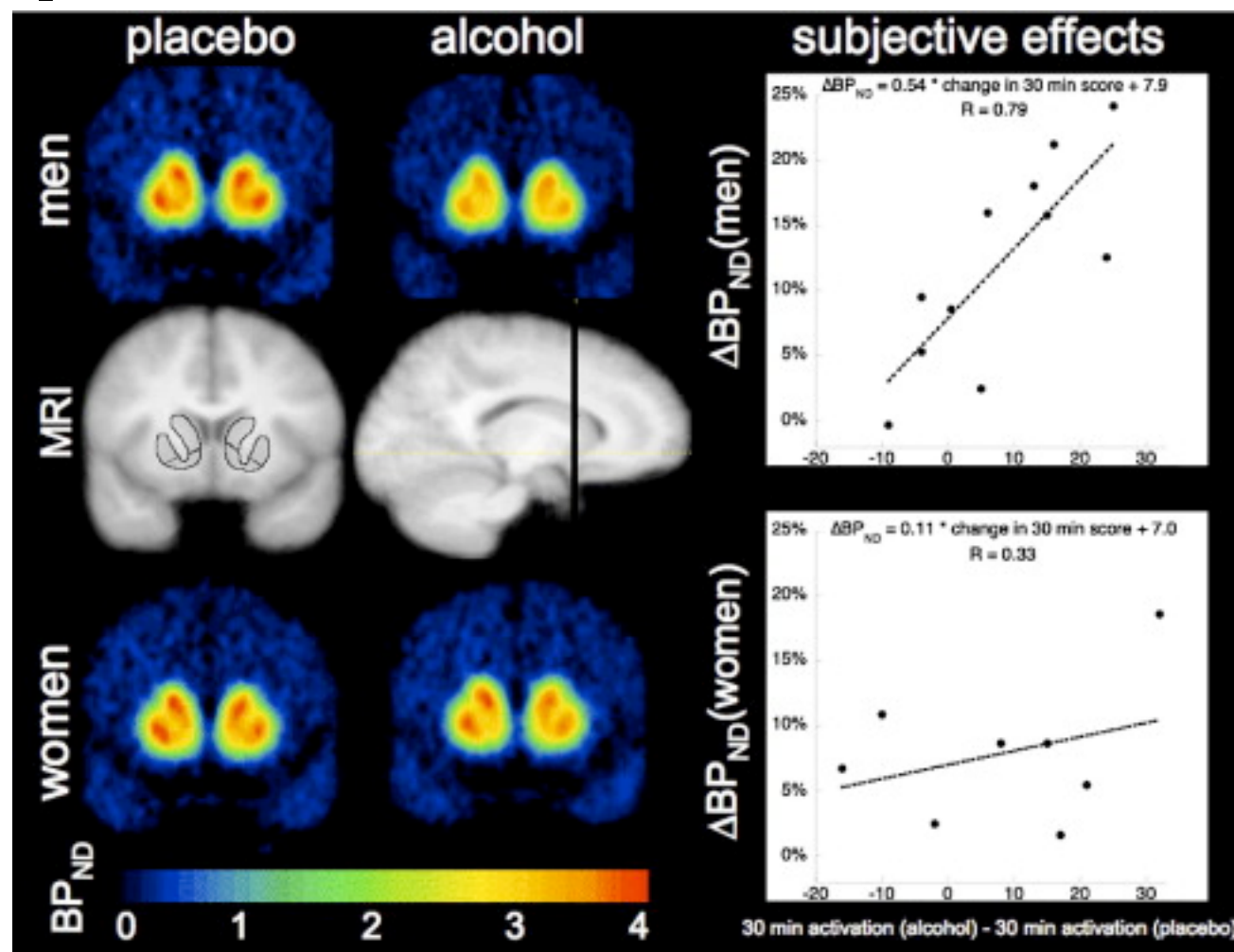
Ingesting household products

- Many products may contain significant amount of alcohol, especially mouthwashes, hand sanitizers, cosmetics
- Poisonings with these products are in young children several fold more frequent than with alcoholic beverages
- The trend is on the increase
- Hypoglycemia is the most common adverse effect
- Seizures and death have occurred
- Lethal dose is thought to be above 6 ml/kg of 100% alcohol ingested in one hour (Mofenson *et al.*, *Emerg Med Clin North Am* 1984; 2, 159-174) or somewhat less (3 g/kg; Vogel *et al.*, *J Toxicol Clin Toxicol* 1995; 33, 25-33) so not very likely with a medical product but not unthinkable with some sanitizers

Drug interactions

- absorption, metabolism
- enhanced psychomotor inhibition with sedatives
- enzyme induction (P450; relevant to phenobarbital, phenytoin, meprobamate, warfarin)
- disulfiram reactions (flushing, tachycardia, nausea, vomiting; cardiac arrhythmias, cardiovascular collapse, respiratory depression, convulsions) possible with simultaneous moxalactam, metronidazole, sulfonamides, chloramphenicol, cefamandole

Dopamine release after administration of ethyl alcohol in humans in dorsal and ventral striatum (PET, [^{11}C]-raclopride)



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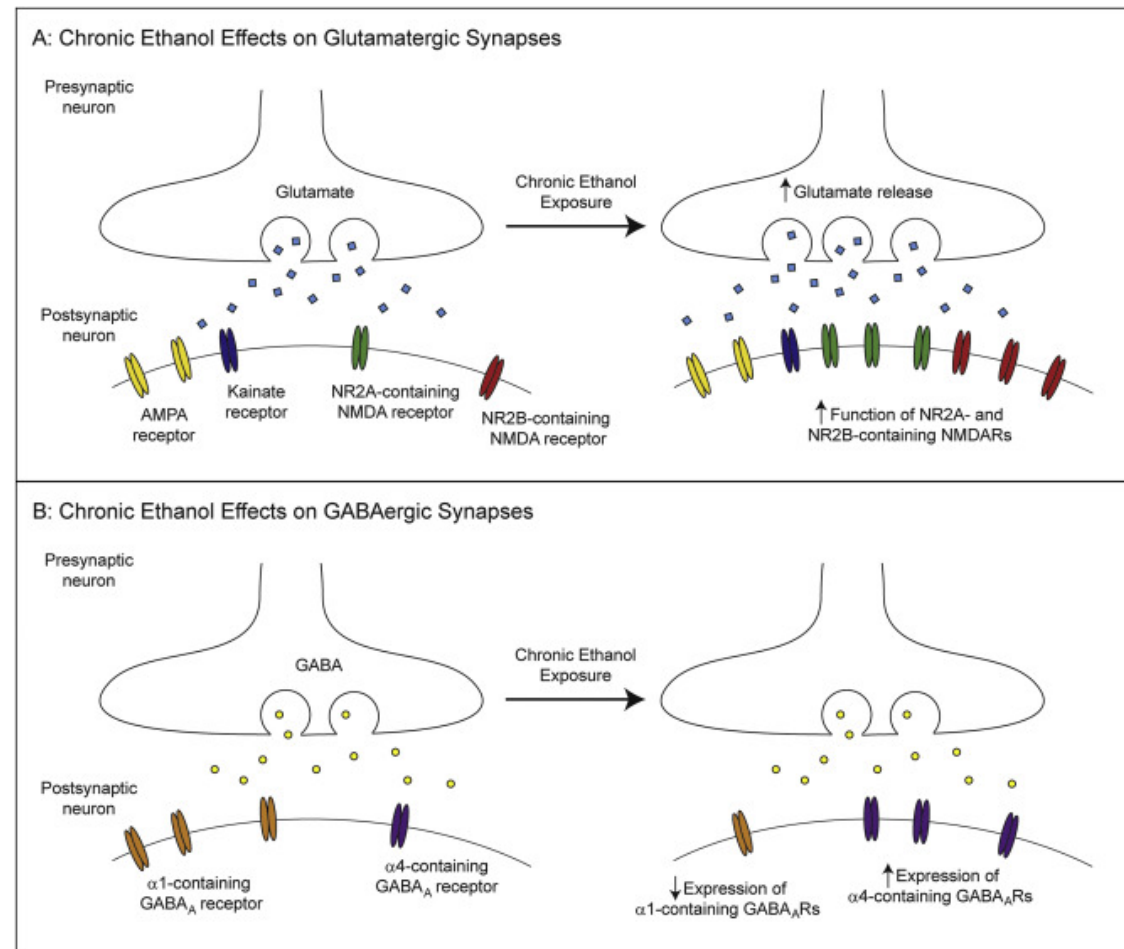
Urban *et al.*, *Biol. Psychiatry* 2010, 68: 689-696)

What happens with adolescent drinking

- In humans (12-18 years)
 - in future drinkers: lower cognitive inhibition and frontal response
 - reduction in attention and visuospatial functioning
 - increases in frontal responses
 - reduction of frontolimbic white matter integrity
- Animal studies (rat 28-42 days)
 - less motor impairment as compared to adults
 - less reduction in Purkinje neuron response
 - reduction in hippocampal volume

Chronic effects of ethanol on GABA- and glutamatergic neurotransmission

- Excitatory glutamatergic neurotransmission is increased
- Complex changes in GABA-ergic neurotransmission
 - release alteration region-dependent (GABA_B)
 - postsynaptic GABA_A receptor composition change



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27

The burden of alcohol use in children

- The study of alcohol use by children <12 years is very limited
- Burden is low in childhood but early use may have long-term consequences



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exposure is changing

with the involvement of gene × environment interactions

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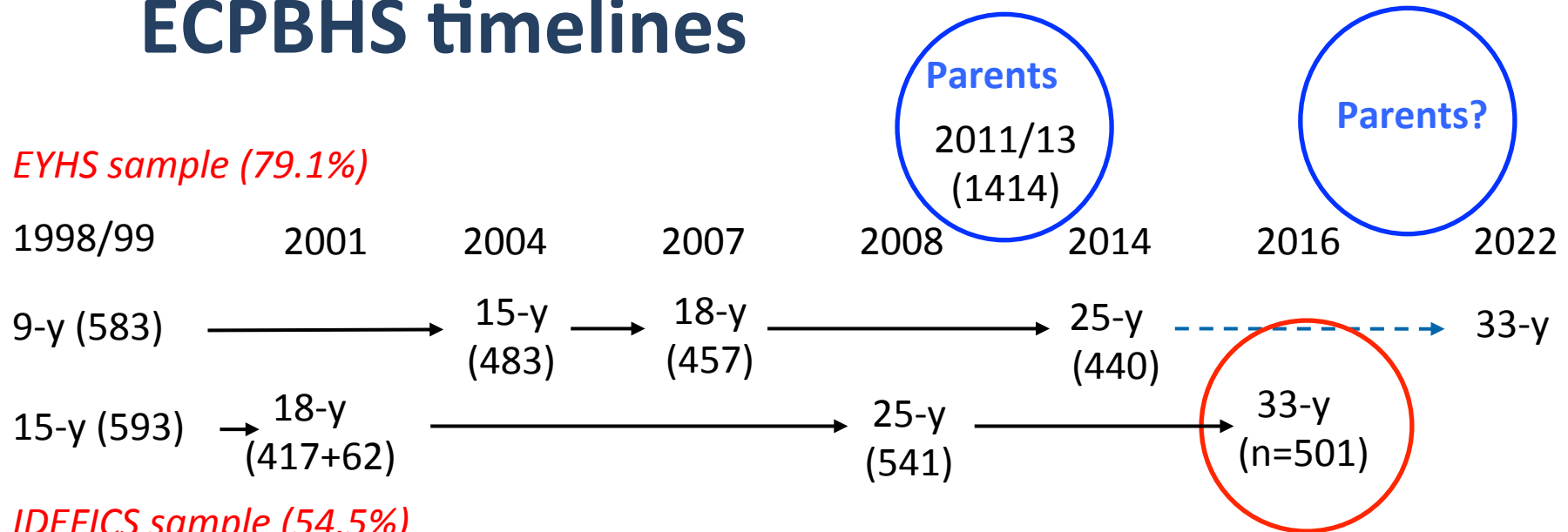
Estonian Children Personality Behaviour and Health Study (ECPBHS)

- Population representative (specifics on EYHS subsample):
 - School as a sampling unit (54 of 56 eligible schools agreed)
 - Probability proportional to school size, 25 schools selected
 - All children of grades 3 and 9 invited, 79.1% participated
 - During the most recent follow-ups, about 80% of the original sample recruited
- (Multi) birth cohort
- Longitudinal (*see below*)
- Multidisciplinary
- Family aggregation
- Estimation of effect size for population

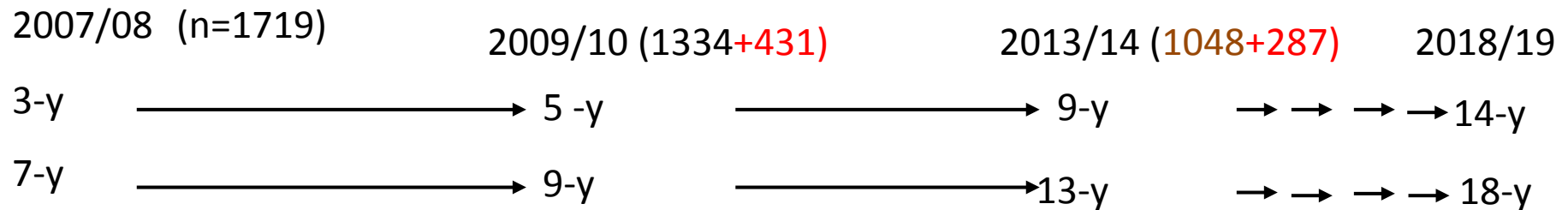


ECPBHS timelines

EYHS sample (79.1%)



IDEFICS sample (54.5%)



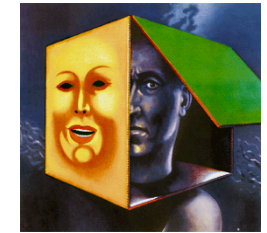
Estonian Children Personality Behaviour and Health Study

www.ecpbhs.ee

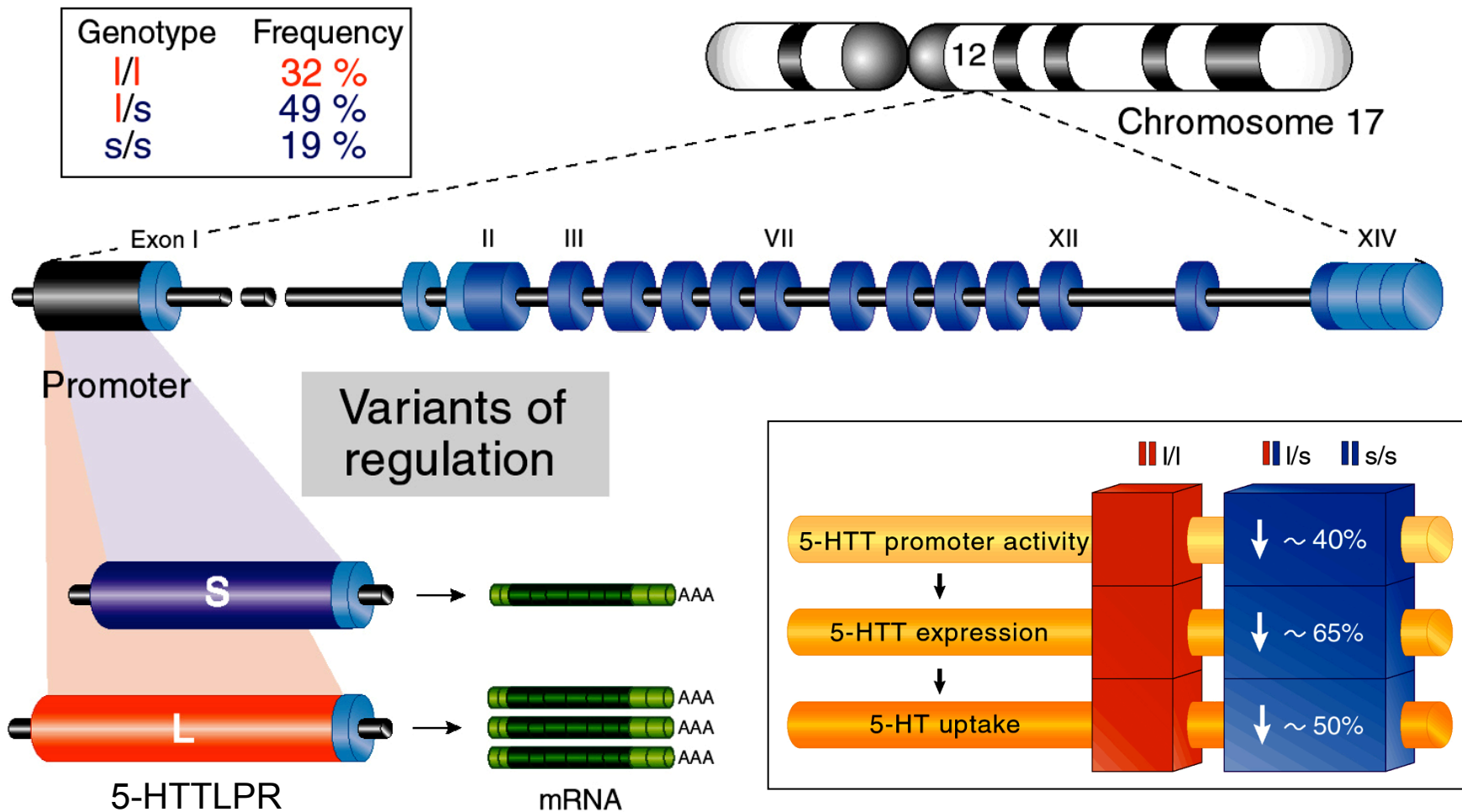
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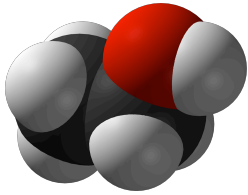
Variation of the Serotonin Transporter Gene: A Tool to Dissect Individual Differences



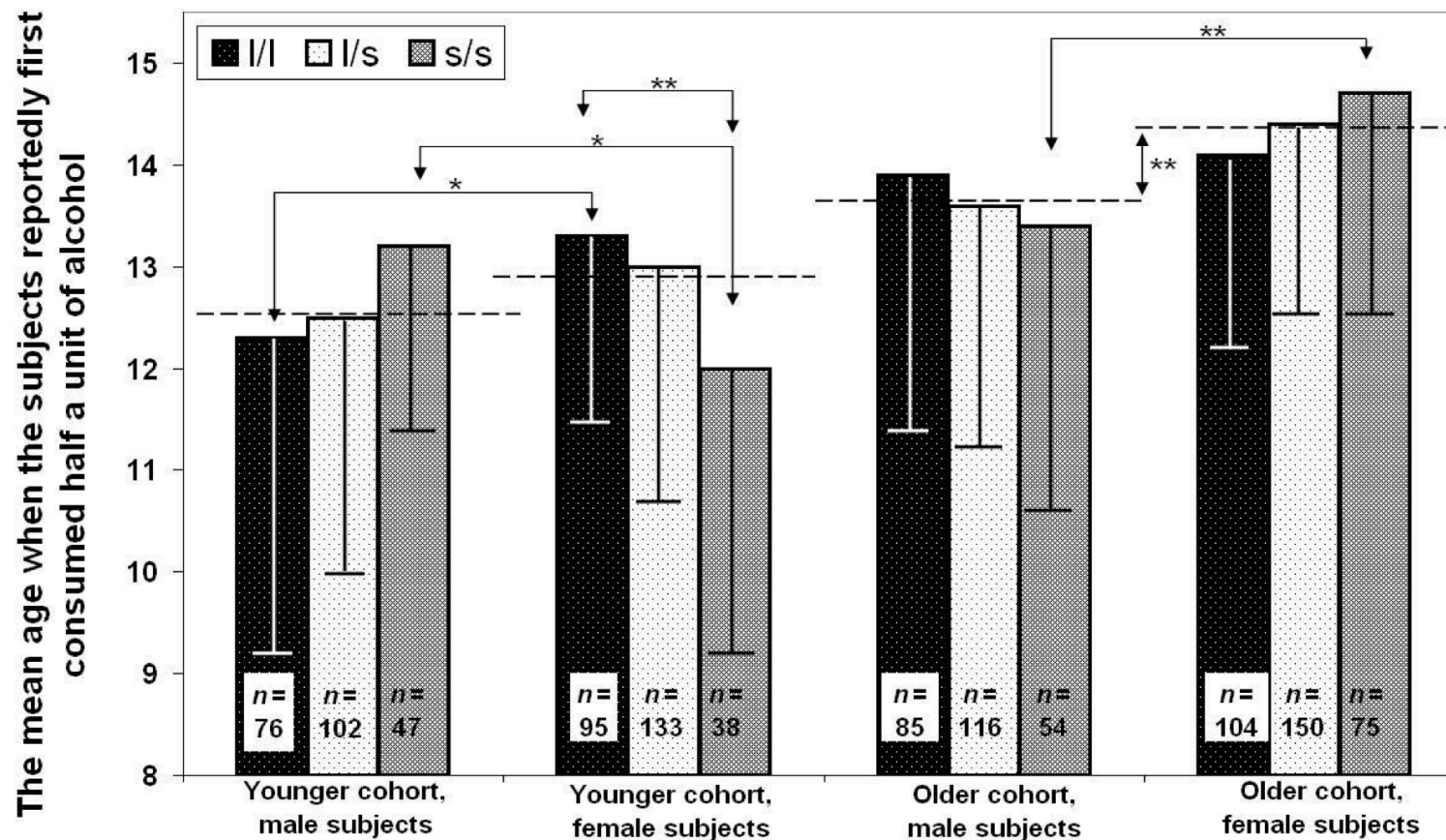
Lesch et al., Science 1996



Courtesy of Klaus-Peter Lesch



Alcohol use is subject to birth cohort effects – and this is 5-HTTLPR dependent



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Vaht *et al.*, *Psychopharmacology* 2014, 231: 2587-2594; Harro & Vaht, in *The Neuroscience of Alcohol*. Elsevier 2018



Conclusively, pharmacology everywhere

- There is a pharmacological agent that
 - is broadly available
 - in a large variety edible and non-edible formats
 - can be consumed involuntarily, accidentally or deliberately
 - is increasingly reported to cause poisonings in children
 - has the potential to be lethal
 - can be involved in iatrogenic cases
 - leads to serious alterations in development of the brain
 - is getting into the organisms of ever younger human beings
- ... and remains part of adult everyday life, sometimes even referred to as *aqua vitae*



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