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Eesti  
tuleviku heaks



# Alkoholi ja aju kohtumiste neurobioloogilised eeldused ja tagajärjed

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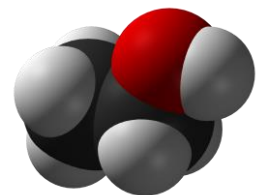
TAI alkoholikonverentsil Viru Konverentsikeskuses 24. septembril 2019





# Etanool: evolutsioon, meditsiin, kultuur

- Hargnemata ahelaga süsivesinik, värvitu ja lenduv
- Pärmseened toodavad võõraste mürgistamiseks, kes tahavad nende toitu ära süüa
- Ravim: meditsiini ajaloos kasutatud paljudel näidustustel, nüüd enamasti asendatud
- Siiski sageli solvent või säilitusaine; ekstsipient paljudes sadades ravimpreparaatides
- Tarbimine on soveldunud inimkultuuri – mitmekülgne tarbimisväärtus
- Toime tõttu ajule

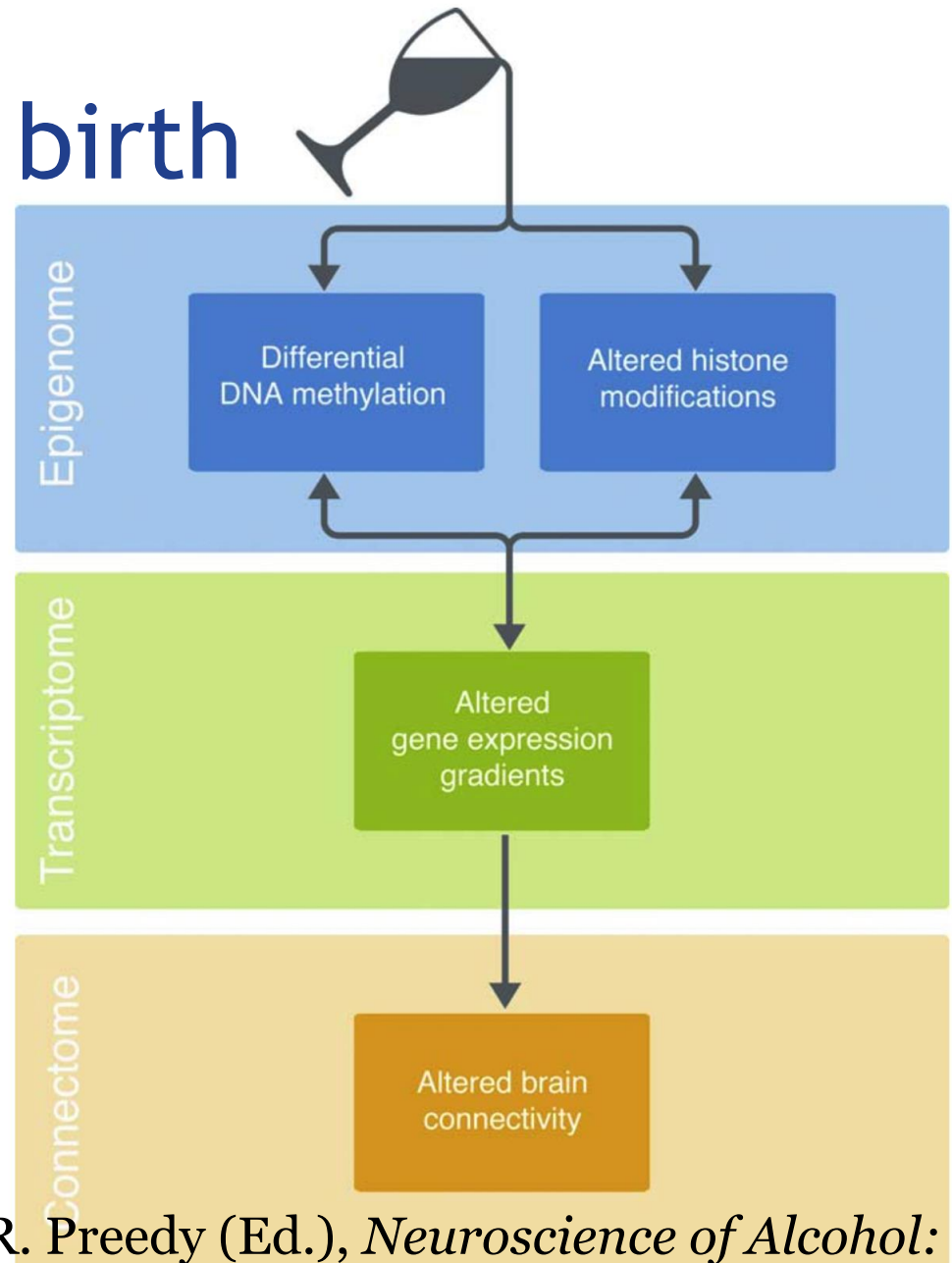




# Even before birth

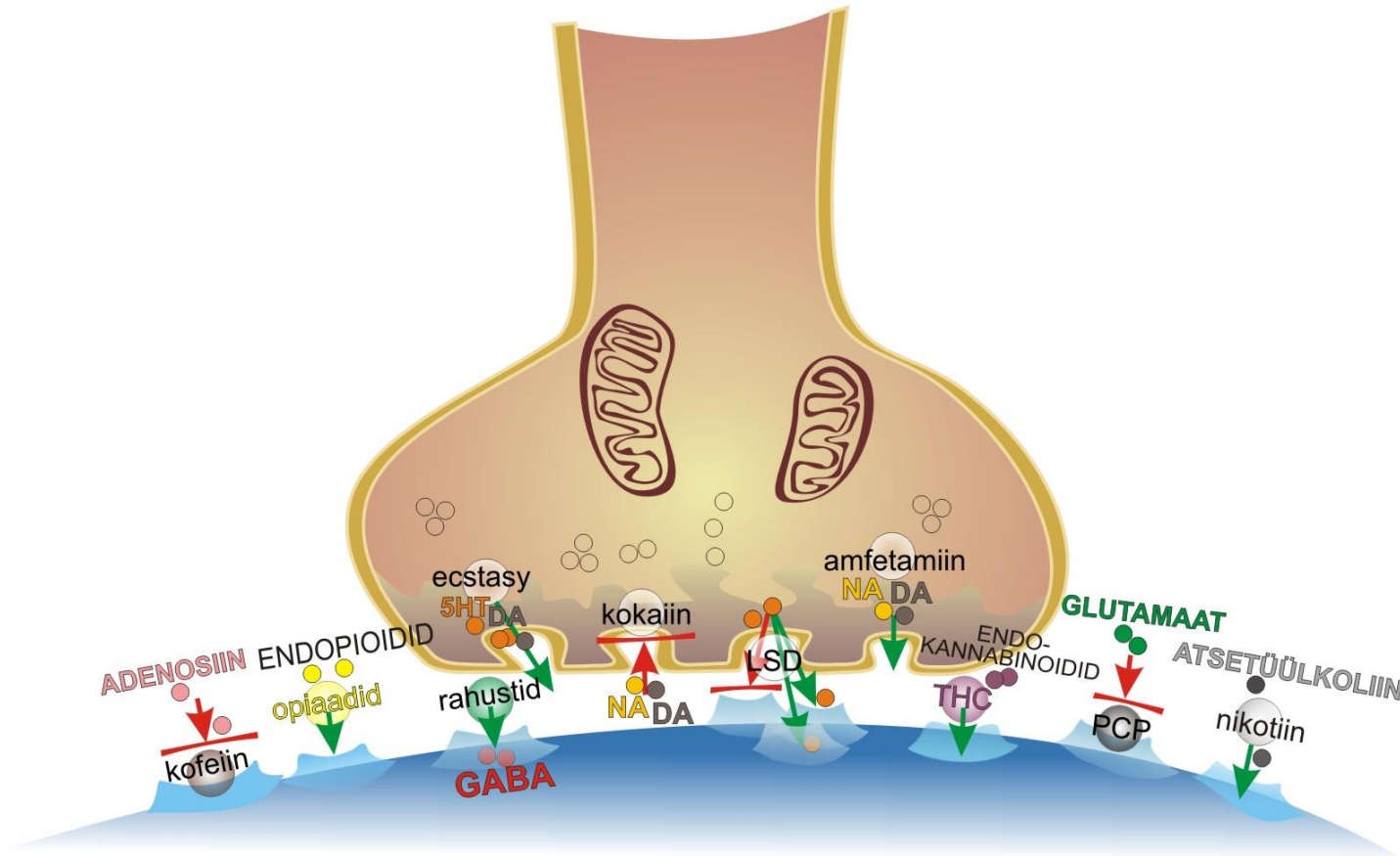
“Beware, thou drink no wine or strong drink ... Lo! thou shalt conceive and bear a son.”

Old Testament, Judges 13:4, 5



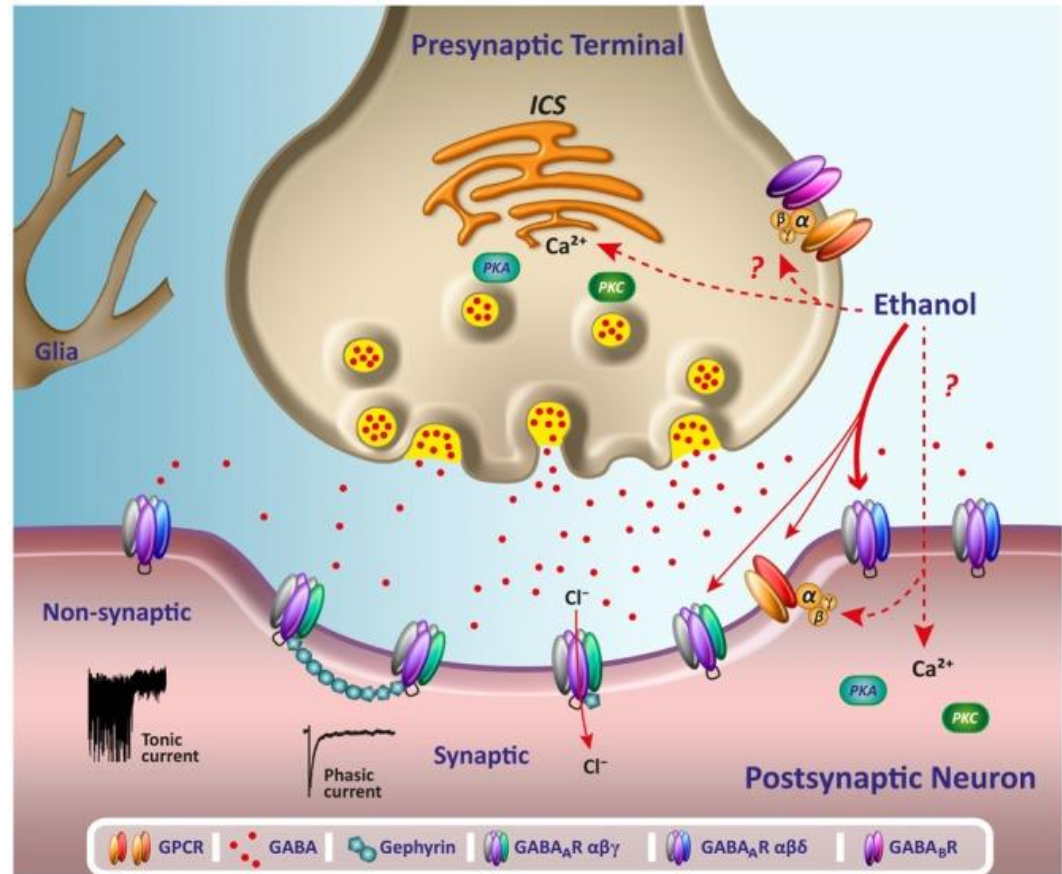
Rohac *et al.*, in: Victor R. Preedy (Ed.), *Neuroscience of Alcohol: Mechanisms and Treatment*. Elsevier 2019; pp. 69-79

# Uimastite esmased molekulaarsed toimemehhanismid on mitmekesised



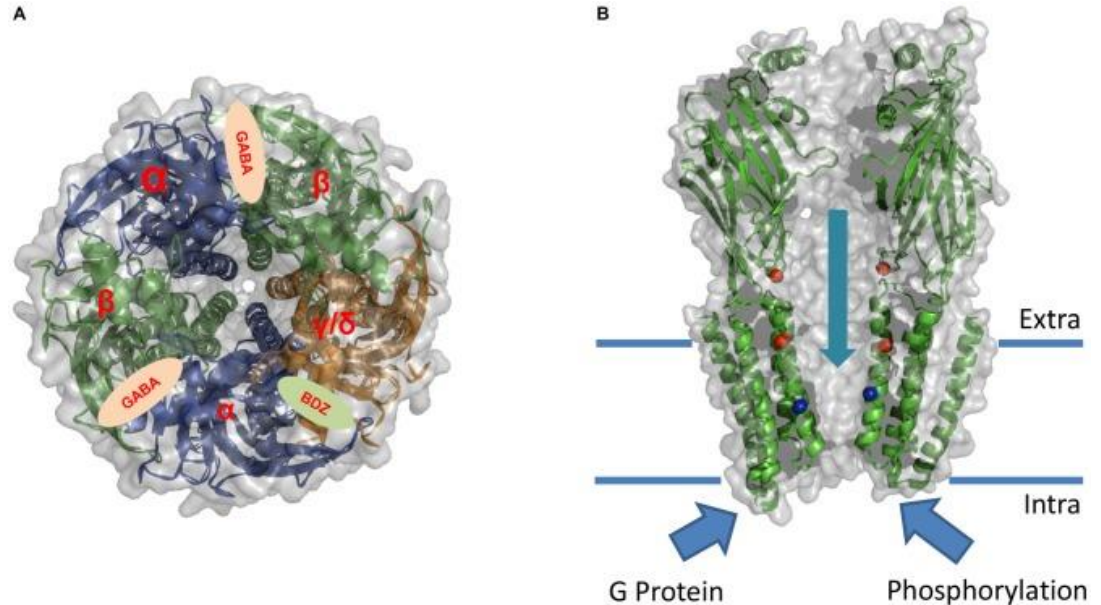
# GABA: the variety of actions of ethanol

- Even at the level of a single neurotransmitter the effects are multiple



# Sites of action for allosteric modulation of GABA<sub>A</sub> receptors

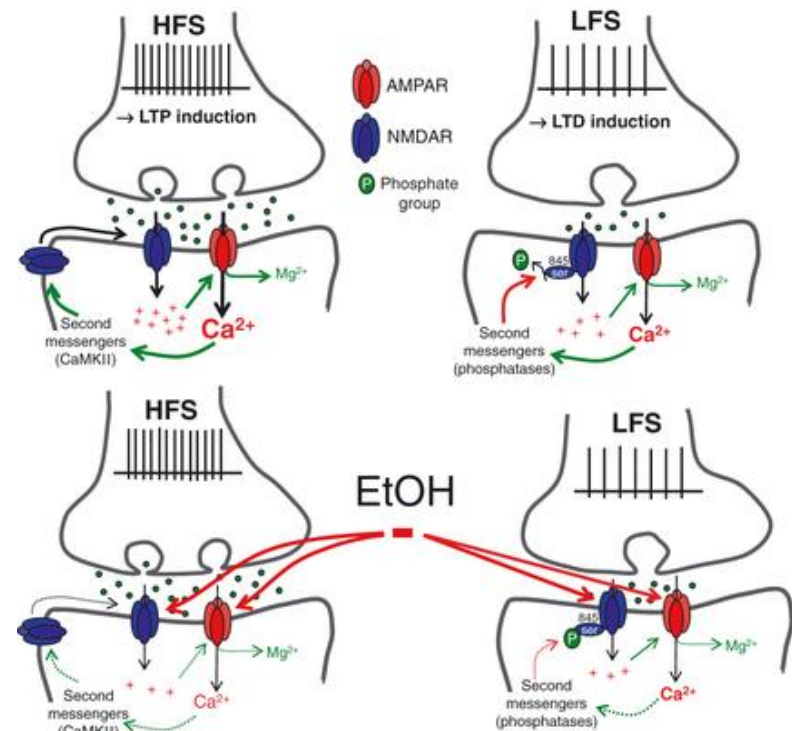
- Some of it we know at minute detail



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

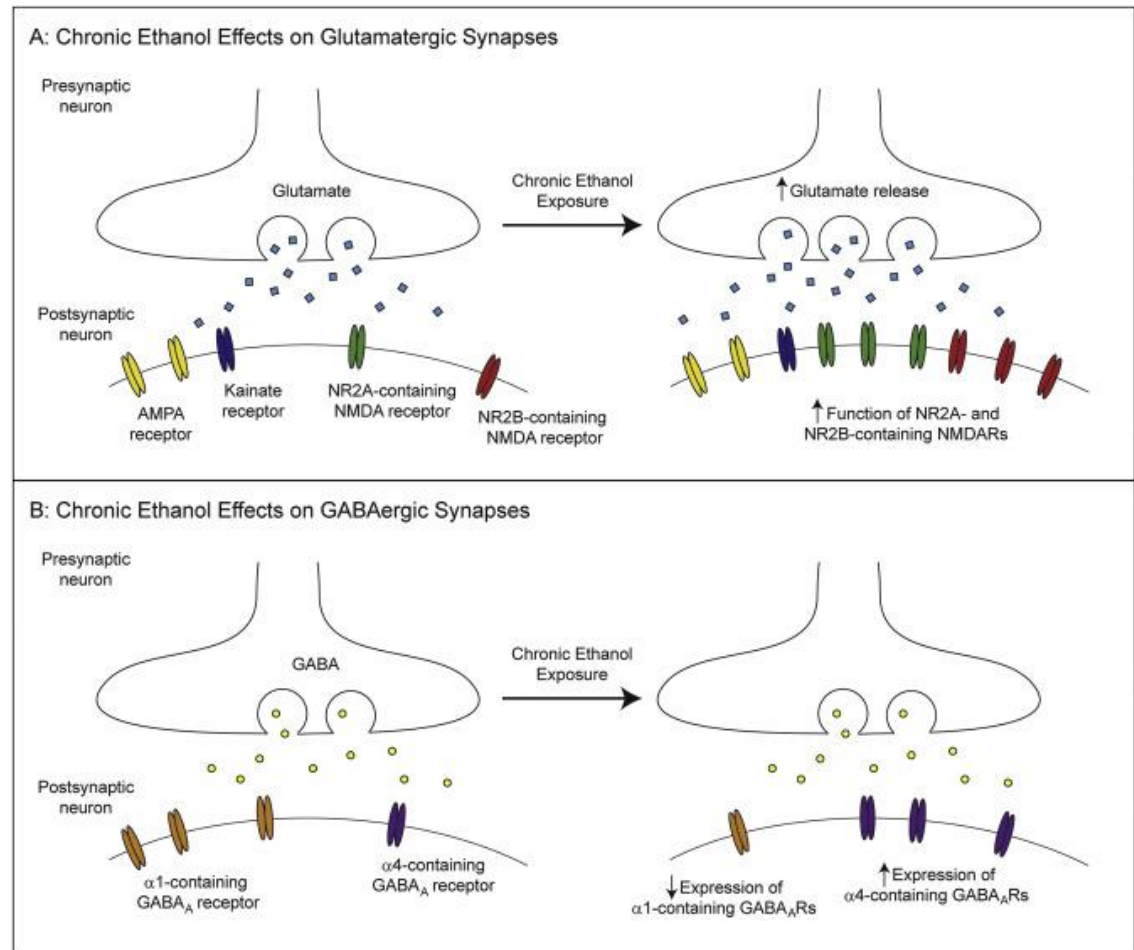
# The other amino acid neurotransmitter: Acute effect of ethanol on glutamate receptors

- 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



# But that was acute effect: Chronic effects of ethanol on GABA- and glutamatergic neurotransmission

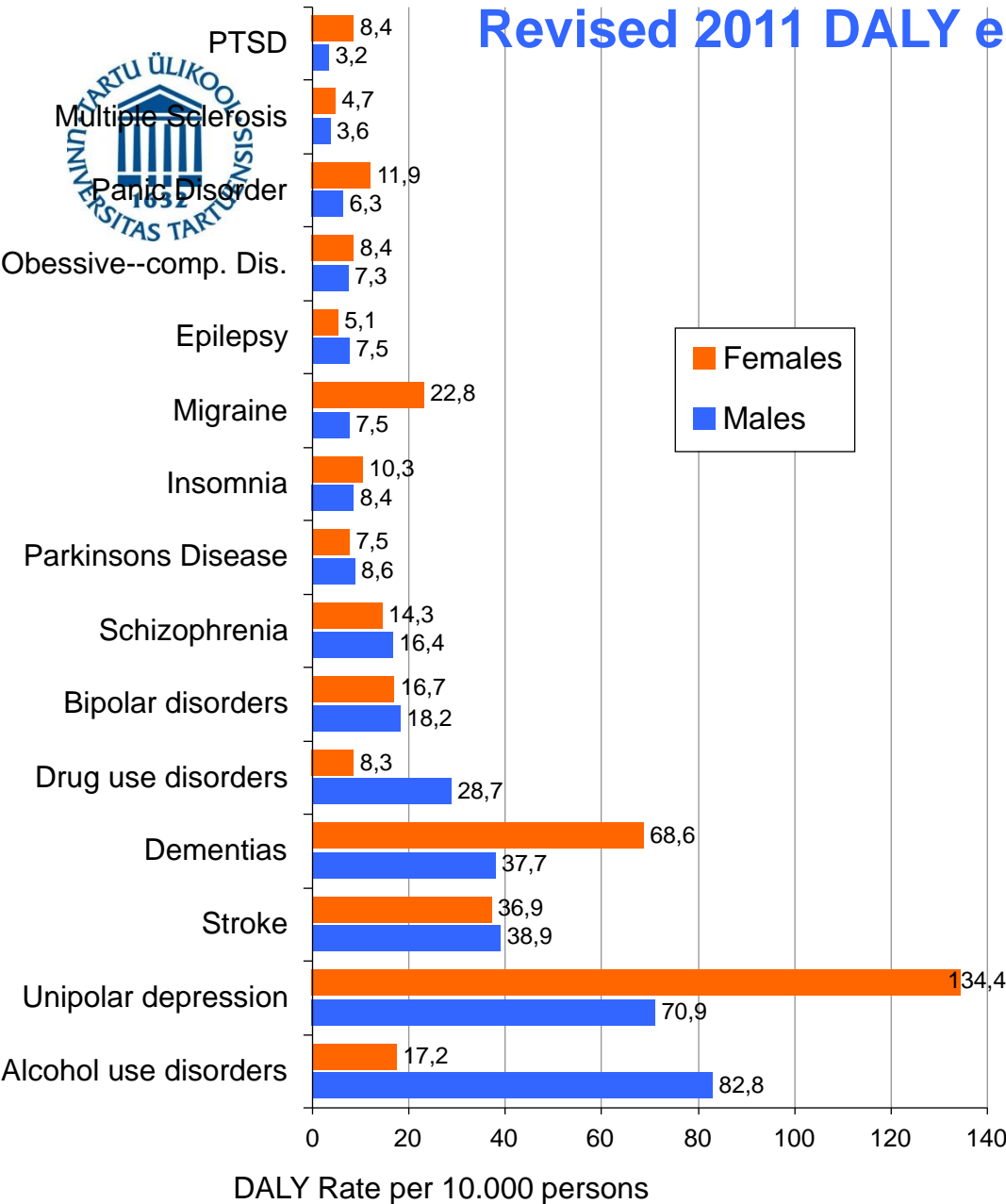
- Excitatory glutamatergic neurotransmission is increased
- Complex changes in GABA-ergic neurotransmission
  - release alteration region-dependent (GABA<sub>B</sub>)
  - postsynaptic GABA<sub>A</sub> receptor composition change



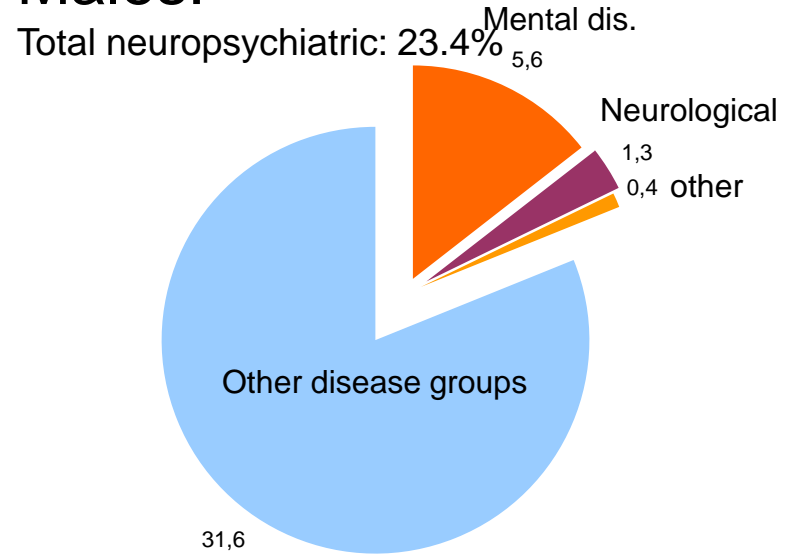




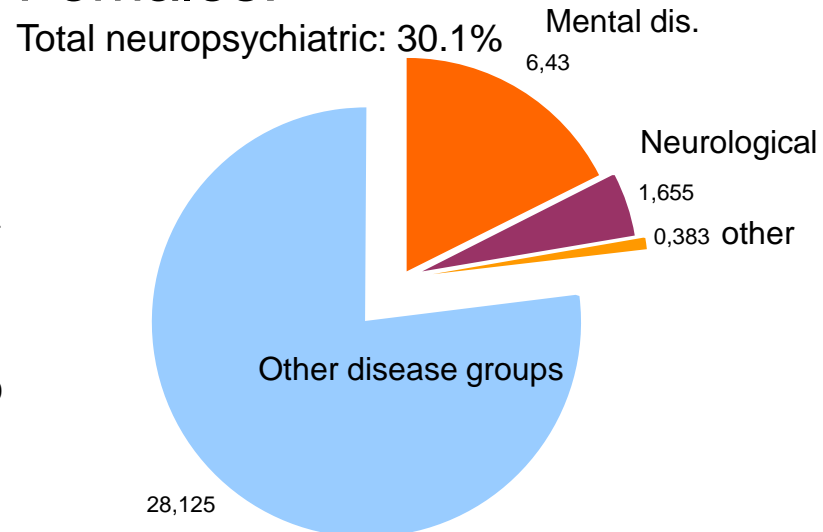
# Revised 2011 DALY estimates: Gender comparison



## Males:

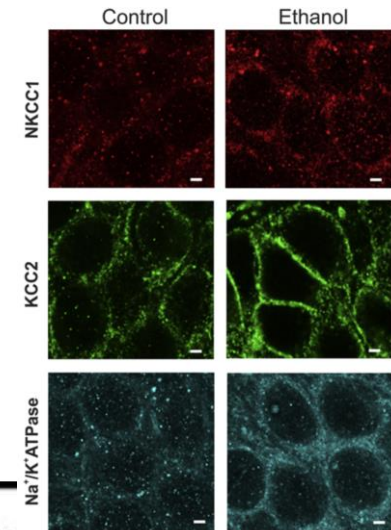


## Females:





# Synaptic effects acute vs. chronic



## Acute synaptic effects

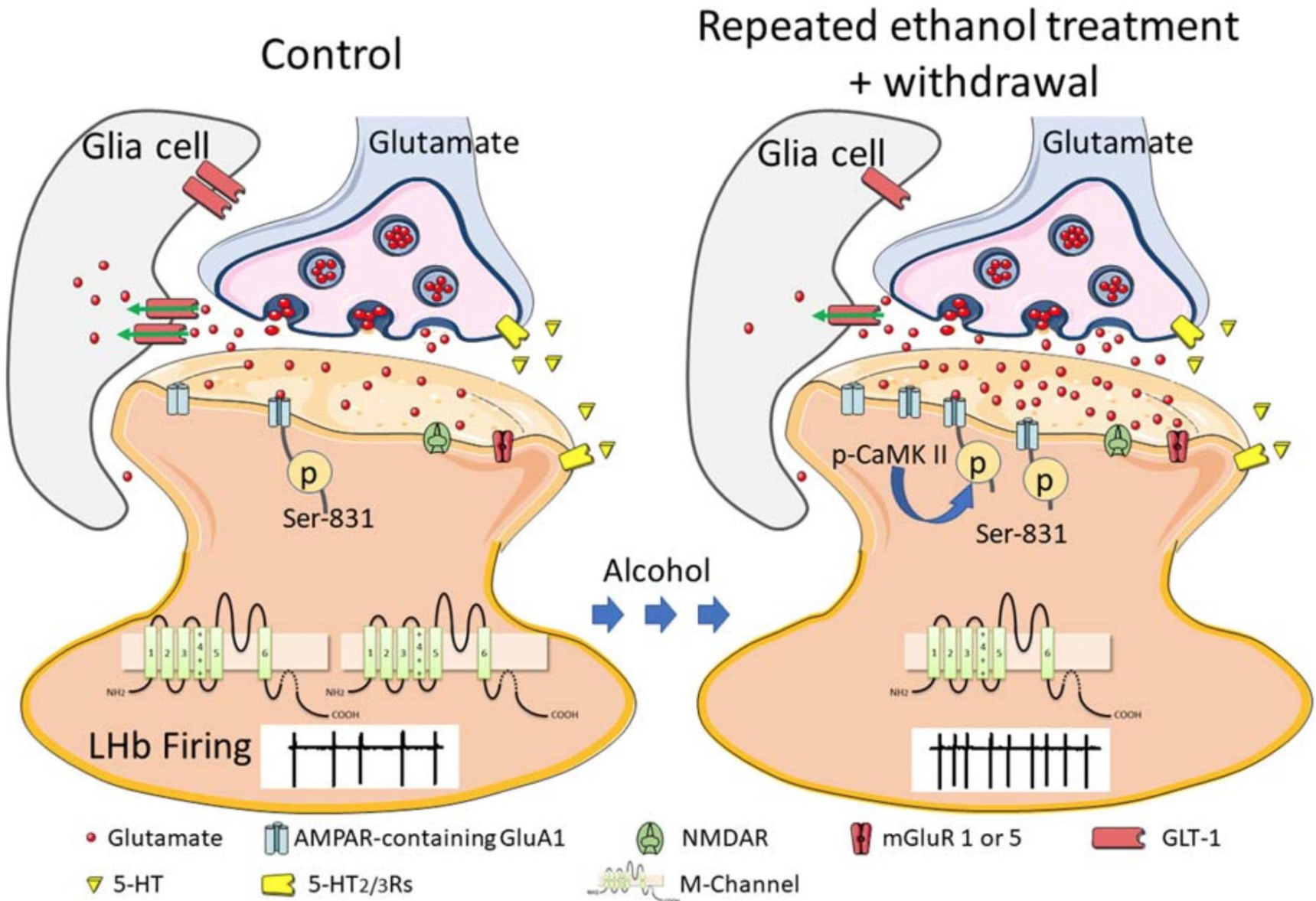
- ↓ Action of  $\alpha 7$  nAChR subtype
- ↓ Neuronal excitability
- ↑ Functionality of many nAChR subtypes
- ↑ Inhibitory function by GABA<sub>A</sub> receptors
- ↑ Excitability (low dosage)
- ↑ Chloride currents through glycine receptors
- ↓ Excitability (high doses)
- Block of excitatory functions by NMDA
- Inhibit ionic currents activated by NMDAR

X

## Chronic synaptic effects

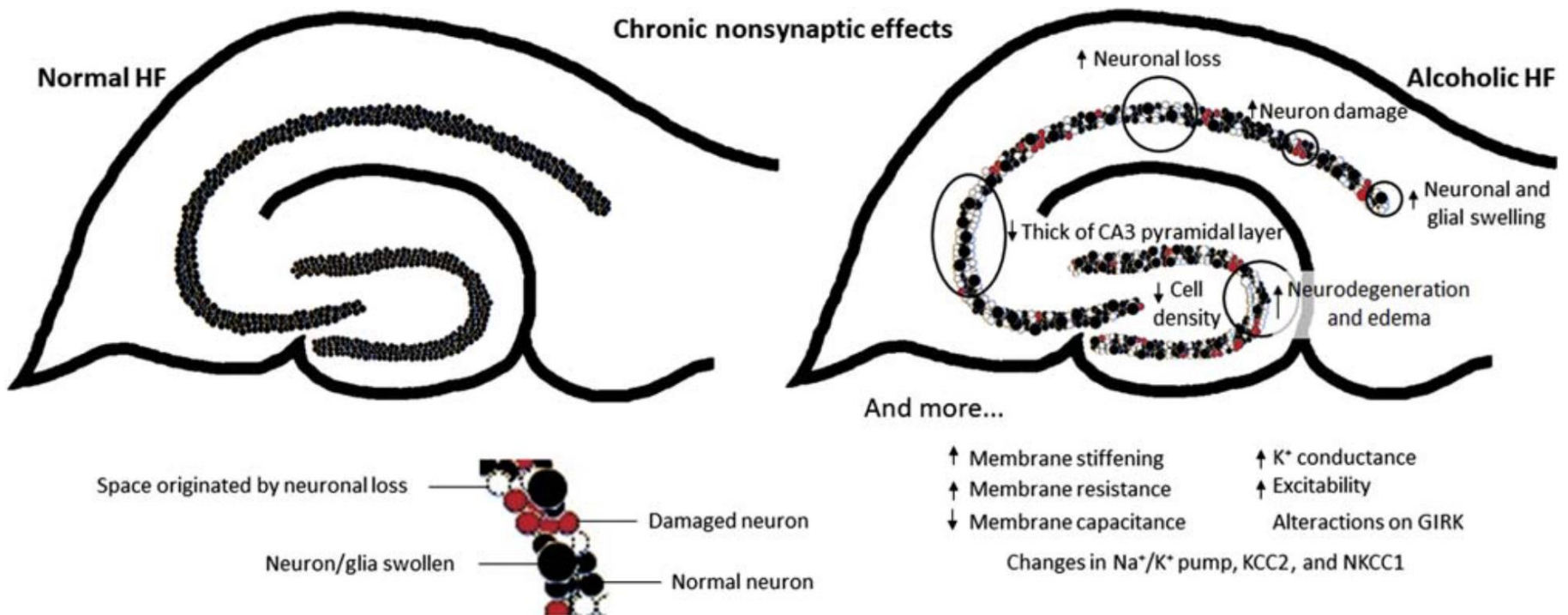
- Alterations on  $\alpha 4\beta 2$  and/or  $\alpha 7$  nAChR subunits
  - ↑ Neuronal excitability
  - ↑ K<sup>+</sup> conductance
  - ↑ Cl<sup>-</sup> conductance
  - Downregulation of GABA<sub>A</sub> receptors
  - ↓ Inhibitory activities
  - ↑ Excitatory activities
  - ↑ Neurodegeneration
  - ↑ Glutamate binding—NMDAR
- { NR1 subtype  
 NR2A subtype

Cupertino Costa *et al.*, in: Victor R. Preedy (Ed.), *Neuroscience of Alcohol: Mechanisms and Treatment*. Elsevier 2019; pp. 131-141



Shiwalkar *et al.*, in: Victor R. Preedy (Ed.), *Neuroscience of Alcohol: Mechanisms and Treatment*. Elsevier 2019; pp. 153-161

# Efektid ei piirdu sünapsitega



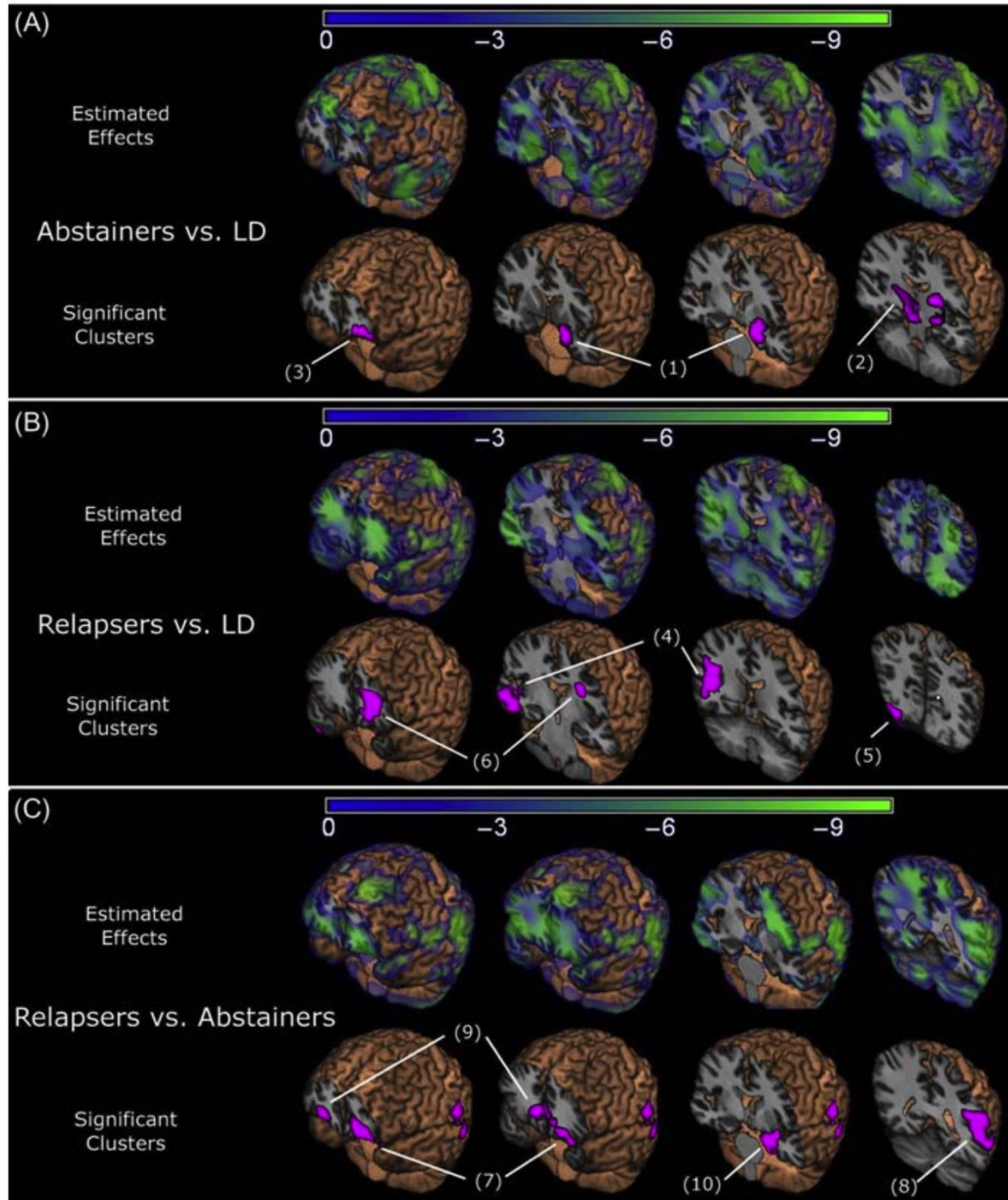
Cupertino Costa *et al.*, in: Victor R. Preedy (Ed.), *Neuroscience of Alcohol: Mechanisms and Treatment*. Elsevier 2019; pp. 131-141



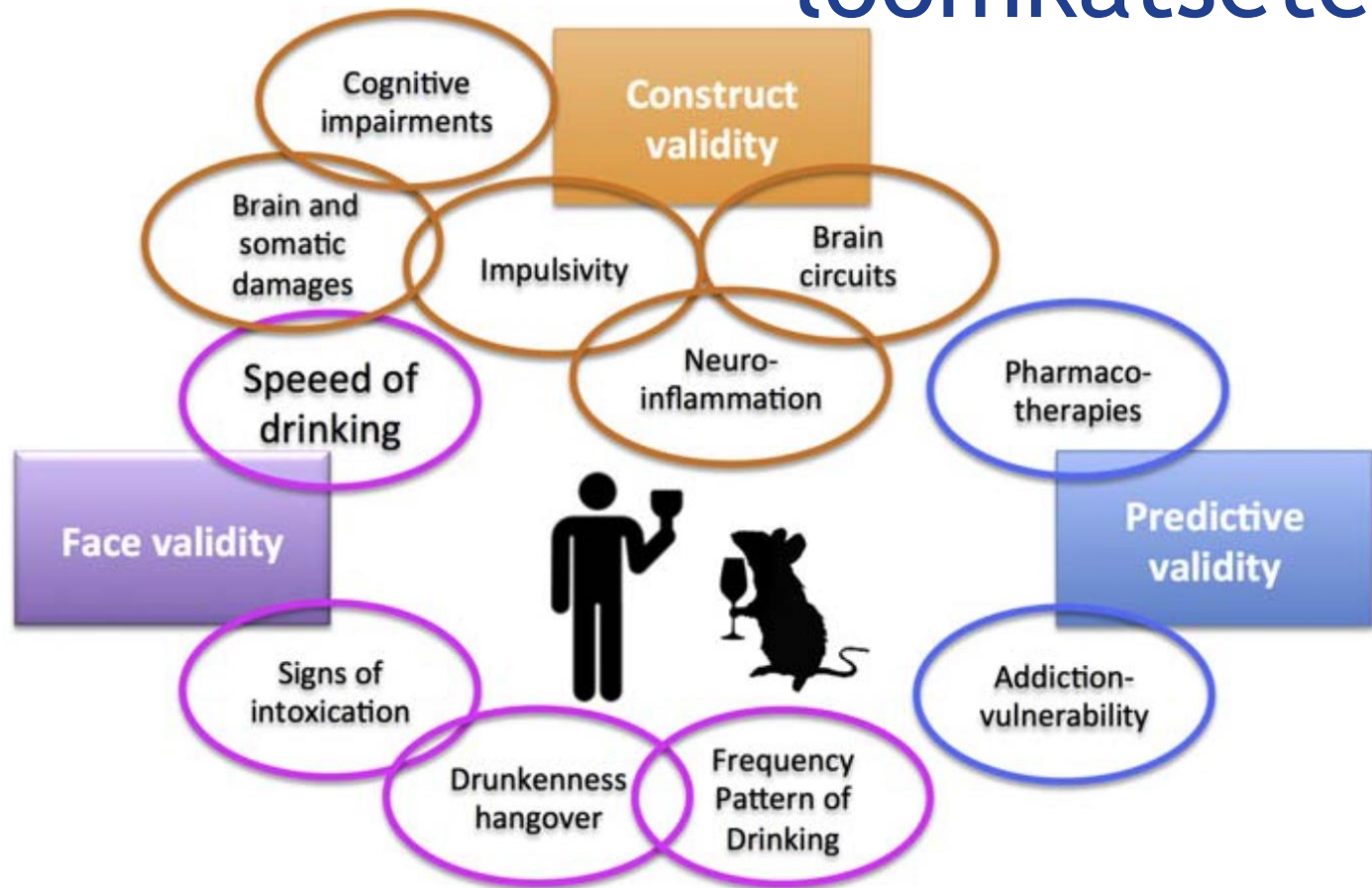
# Aju on muutumises

- A: mandelkeha, hippokampus, entorhinaalkorteks, taalamus, ümbritsev valgeaine; taalamus, OFC
- B: oimusagara keskosa/insula, kuklasagar, *corona radiata superior*
- C: orbitofrontaalsed, temporaalsed piirkonnad, mandelkeha/hippokampus/taalamus

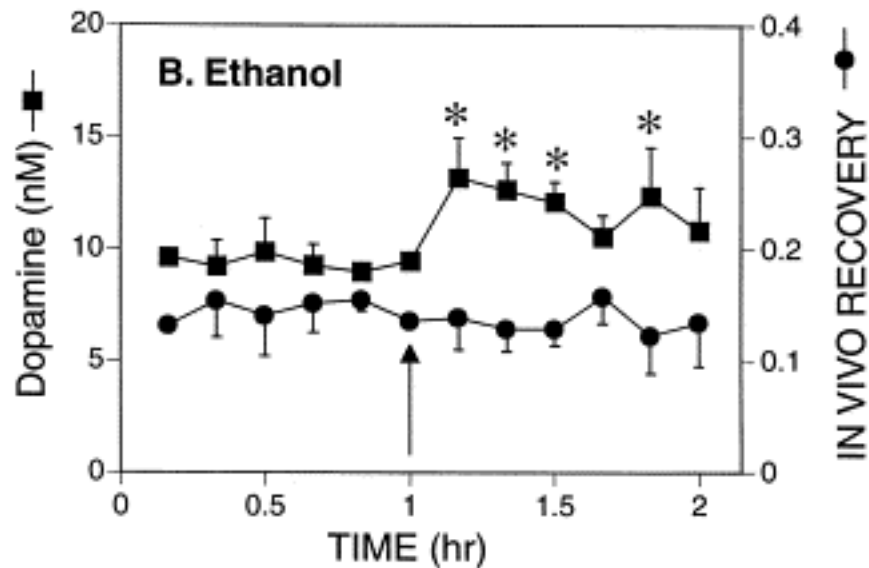
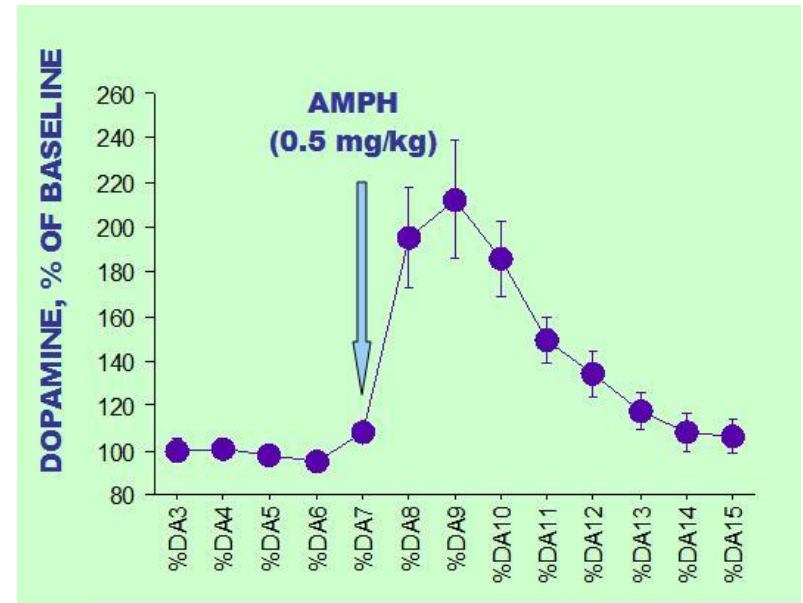
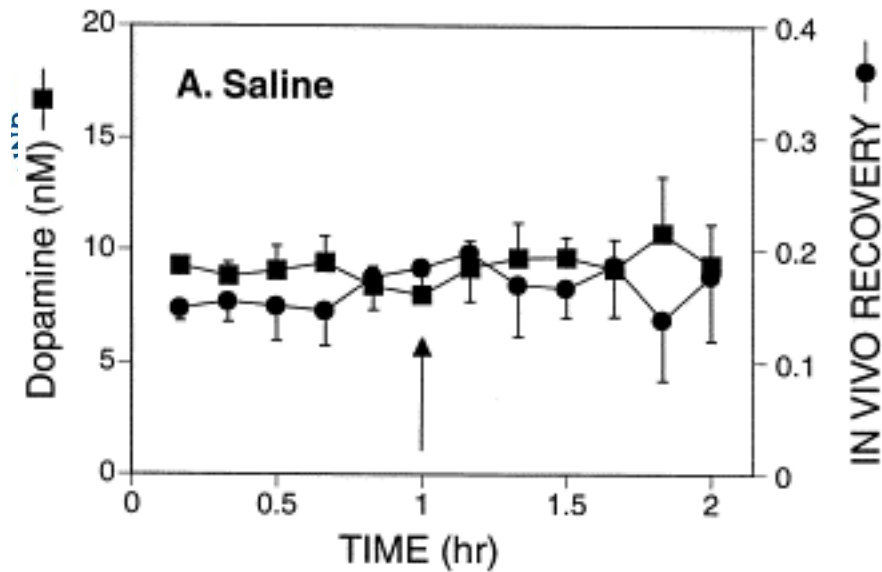
Cardenas *et al.*, *Biological Psychiatry* 2011; 70, 561-567



# Suur osa teadmistest tänu loomkatsetele



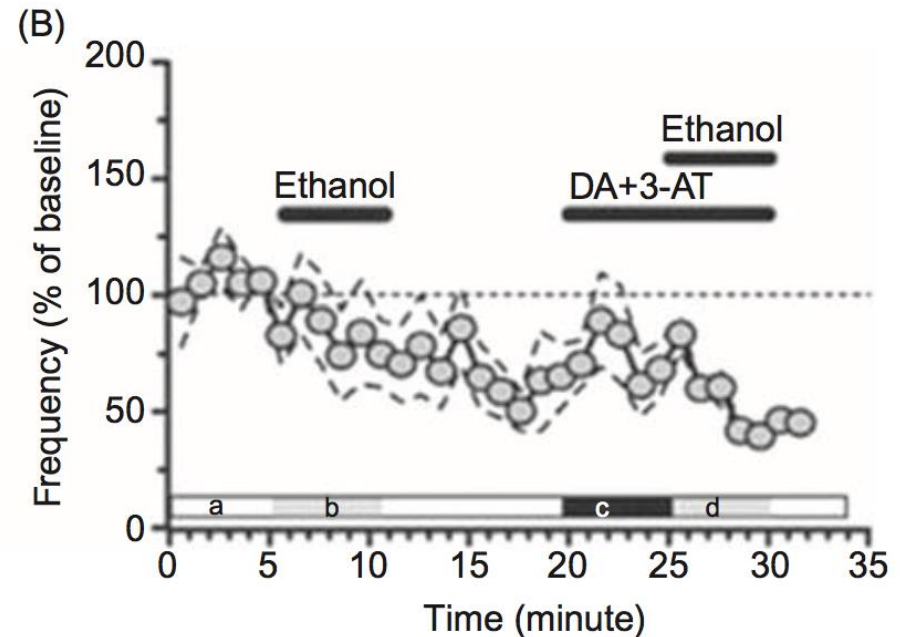
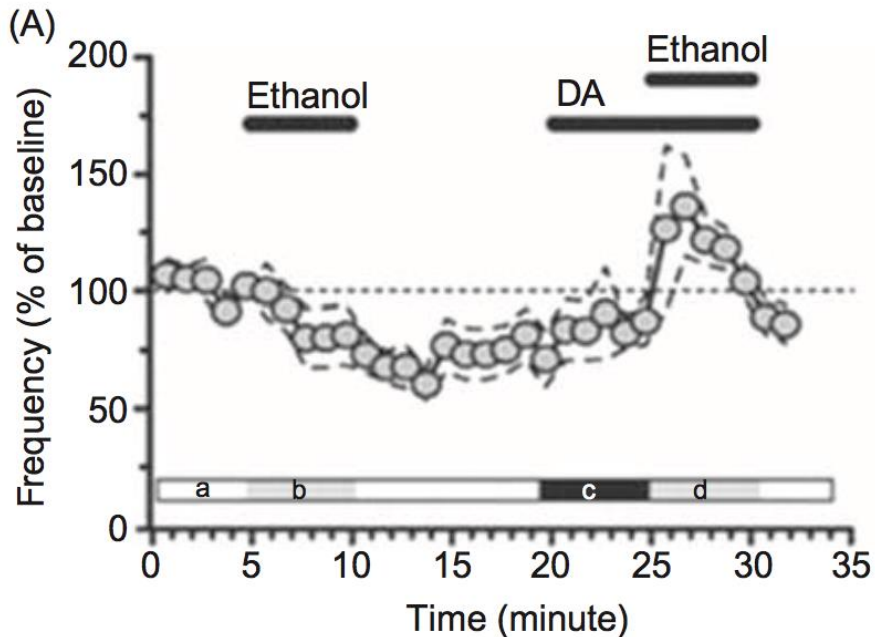
Jeanblanck *et al.*, in: Victor R. Preedy (Ed.), *Neuroscience of Alcohol: Mechanisms and Treatment*. Elsevier 2019; pp. 57-66



Dopamine release in nucleus accumbens after ethanol (1 g/kg) in rats (Yim & Gonzales, *Alcohol* 2000; 22, 107-115)

Dopamine release in nucleus accumbens after ethanol (1 g/kg) in rats (Yim & Gonzales, *Alcohol* 2000; 22, 107-115)

# Etanooli metaboliitide roll dopamiinitõusus

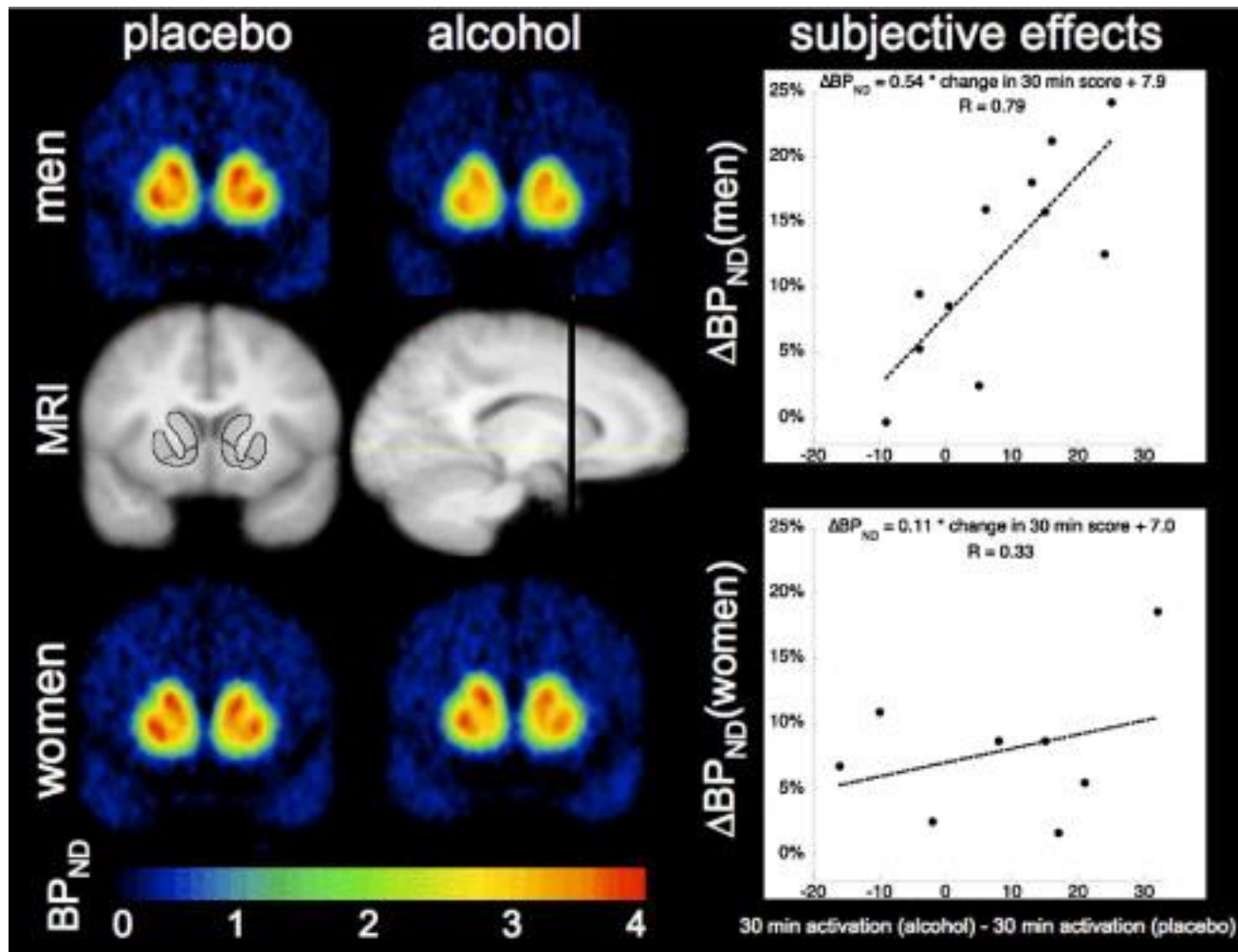


- A: etanooli toime VTA neuronitele sõltub dopamiinist (AMPT hiired)
- B: atsetaldehyüdi moodustumine on katalaasi inhibitoriga takistatud, siis ei teki reaktsiooni dopamiiniga ja salsolinooli





# Dopamine release after administration of ethyl alcohol in humans in dorsal and ventral striatum (PET, [<sup>11</sup>C]-raclopride)

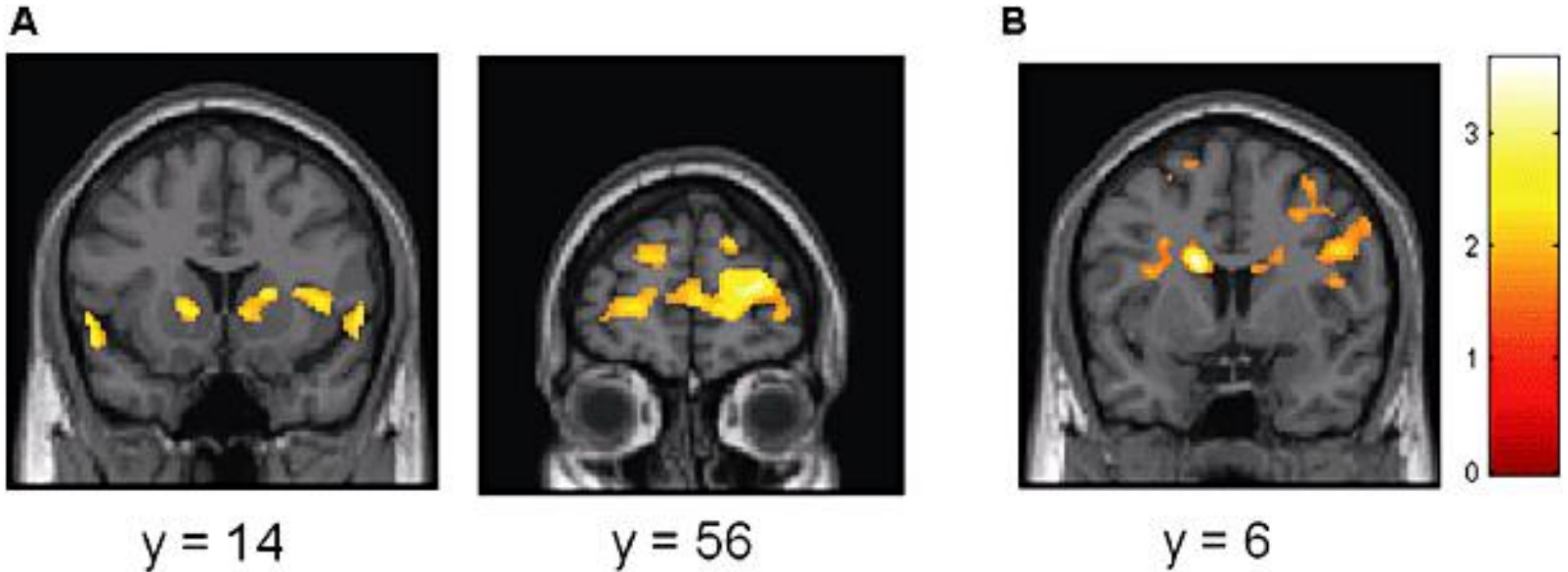




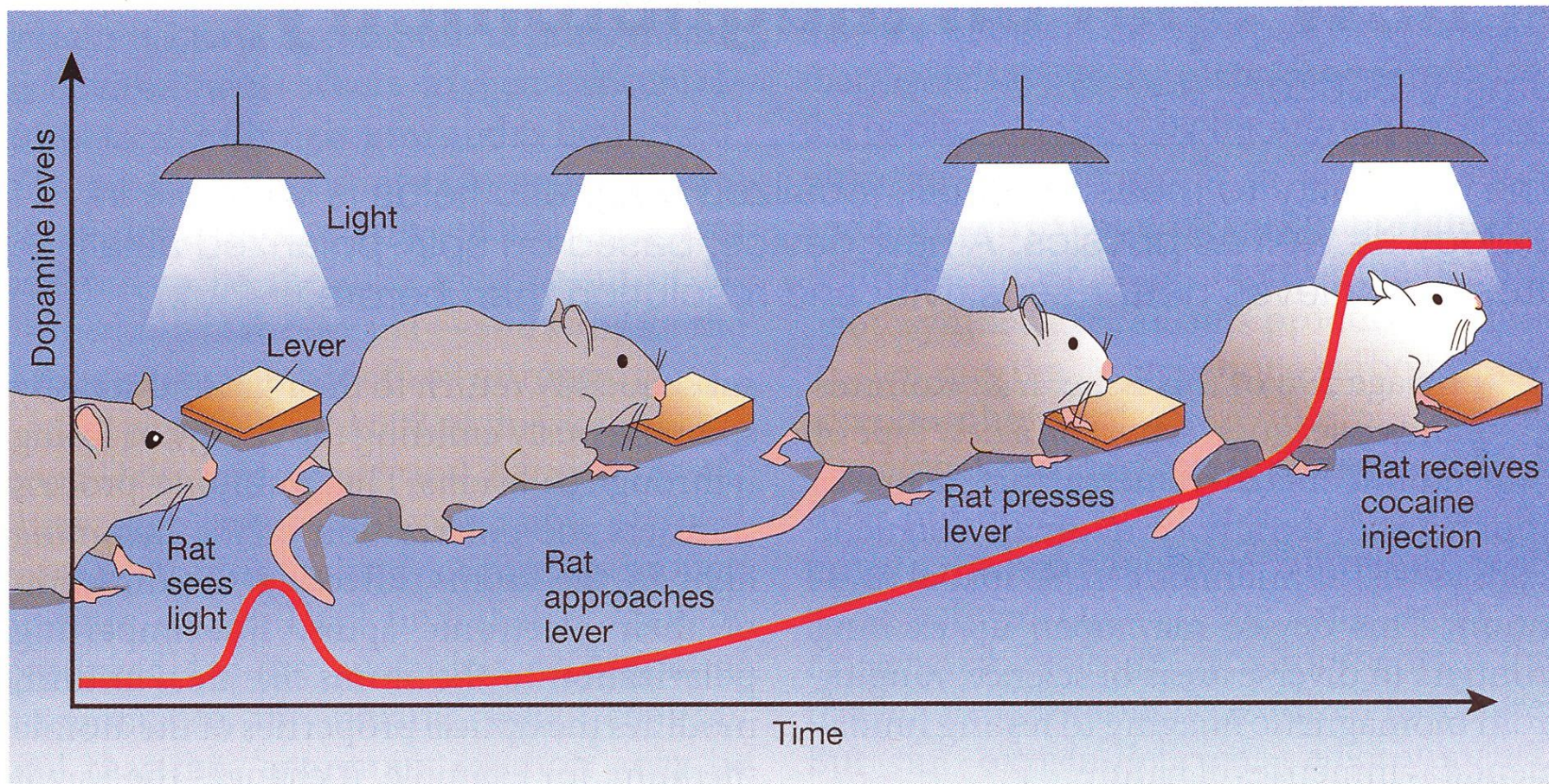
Tüüpiline oopiumiurgas  
XIX - XX sajandi-vahetuse  
Pariisis

*Le Petit Journal* kaas 5.07.1903

# Mõõdukad ja liialdavad *social drinkers*: aju ärgastumine alkoholi nägemisel



- (A) Mõõdukail ärgastuvad ventraalne juttkeha ja prefrontaalne korteks;  
(B) liialdajail ärgastub peamiselt dorsaalne striatum (Vollstädt-Klein *et al.*, *Addiction* 2010, 105: 1741-1749)



Dopamiin nii tugevdab ihaldatava otsimist kui ka vabaneb selle kättesaamisel (Self, *Nature* 2003, 422: 573-574)

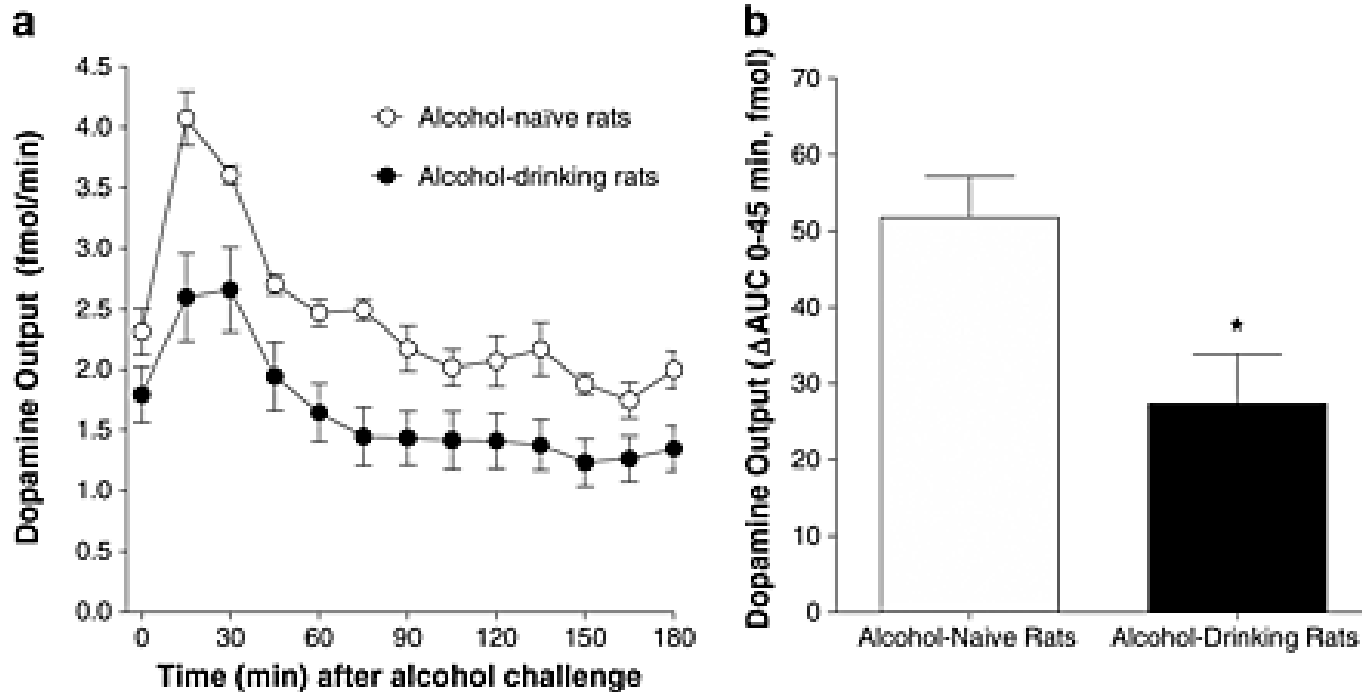


# SÕLTUVUSHÄIRETE TEKE I

- uimastid leevendavad võõrutusnähte ja aitavad põgeneda meeldivamasse “tegelikkusesse”
- sõltuvus tekib uimasti korduval kasutamisel püsivate ja süvenevate muutuste kujunemisel ajus
- mida korduvam uimasti kasutamine, seda väljendunumad muutused aju keemias ja inimese käitumises
- uimastid ärgastavad ajus närvirajad, mis kulgevad keskajust eesajju ja kasutavad virgatsainena dopamiini



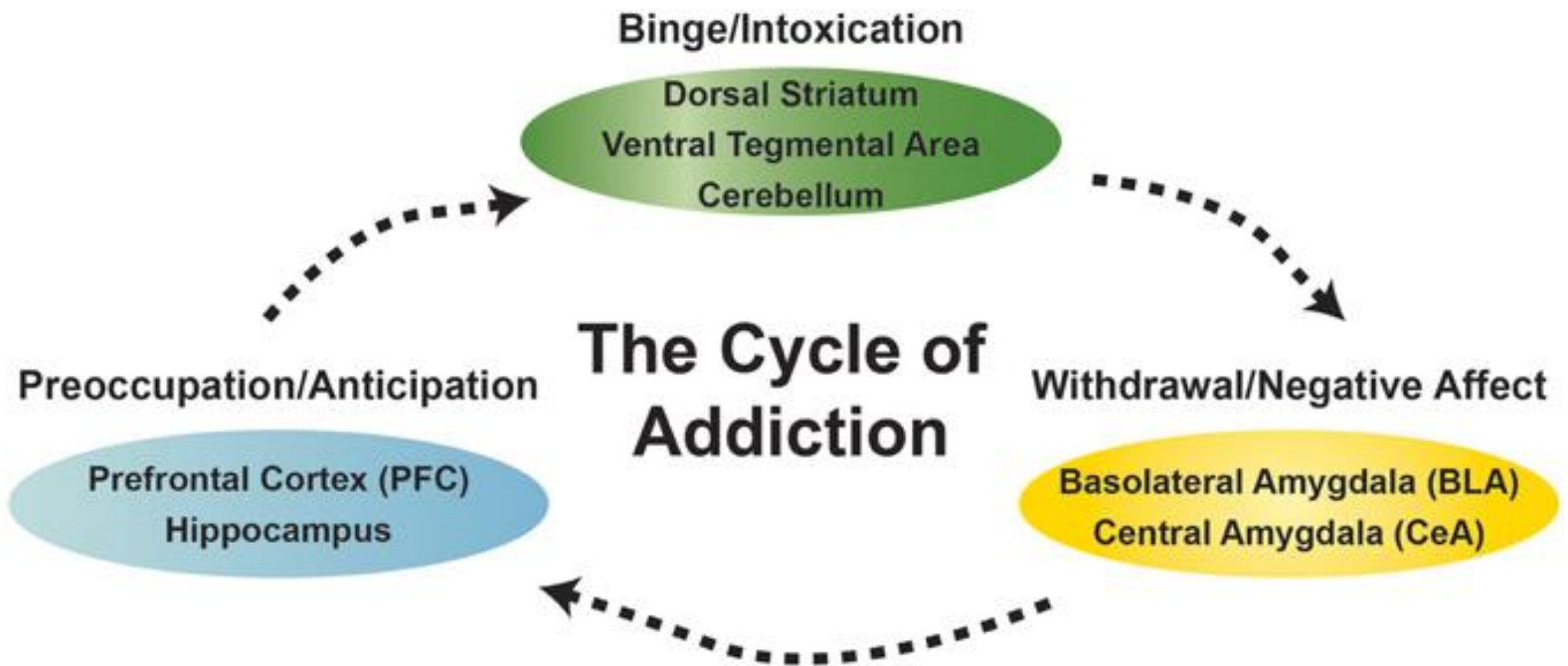
# Dopamiini vabanemise vähenemine joodikroottidel



Feltmann *et al.*, *Addiction Biology* 2016; 21, 438-449



# Sõltuvuse neuropsühholoogia lihtsustatult



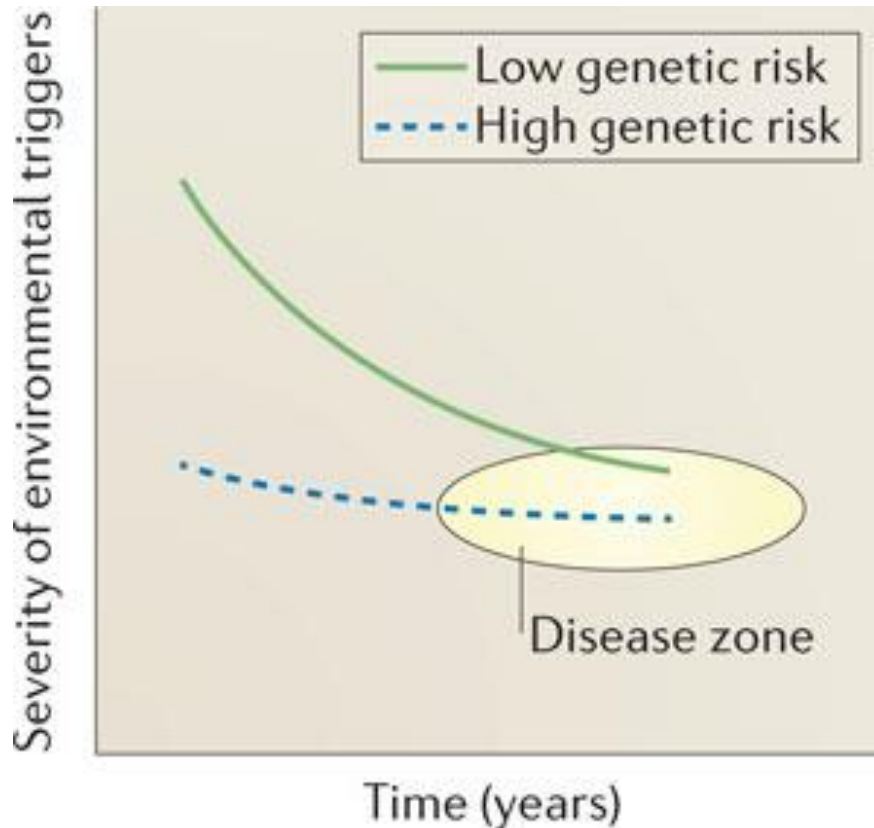


# SÕLTUVUSHÄIRETE TEKE II

- need närvirajad tegelevad olulisuse omistamisega kogetule ilma teadvuse osavõtuta – nii muutuvad uimastid ja nendega seostuv OLULISIMAKS
- uimasti korduval kasutamisel leiab aset assotsiatiivne õppimine – uimastiga seostuv hakkab kontrollima käitumist, paneb uimasteid ihaldama
- iha ja meeldimine on eristatavad
- kõnealused muutused on püsivad, ja mõnikord on nad pöördumatud



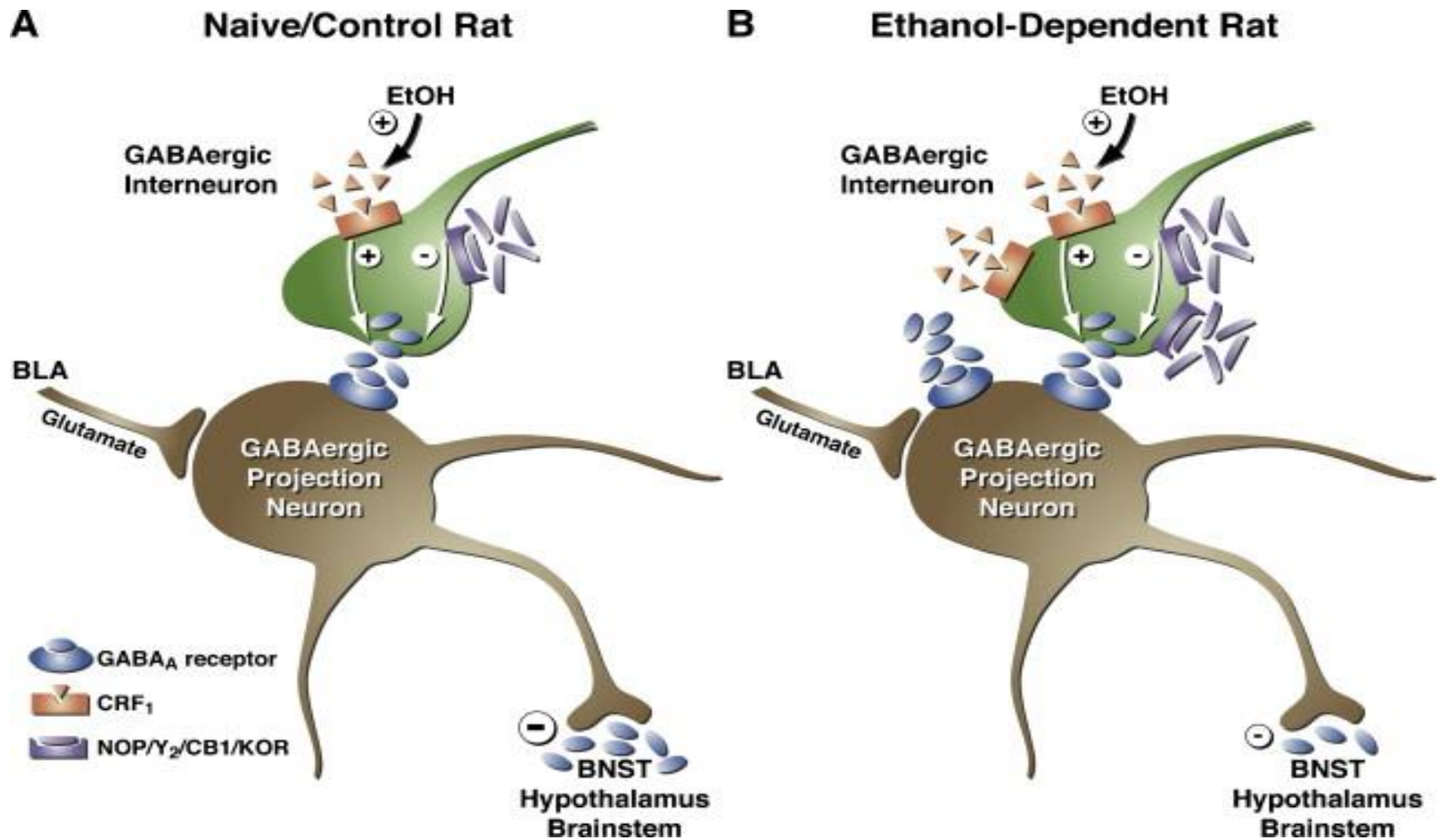
# Keskkonna tähendus sõltub geenivariantidest



- Alkoholism enamasti kujuneb aeglaselt, sotsiaalse joomise foonil
- Aja jooksul väheneb vallandava faktori vajalik tugevus
- Geneetiline eelsoodumus toob kaasa varajase tundlikkuse keskkonnategurite suhtes

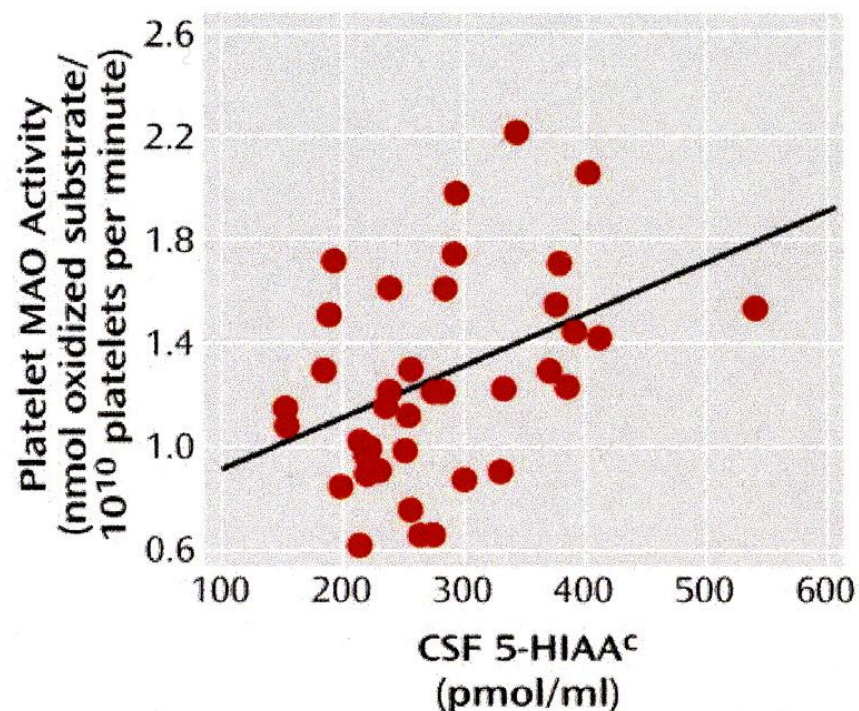
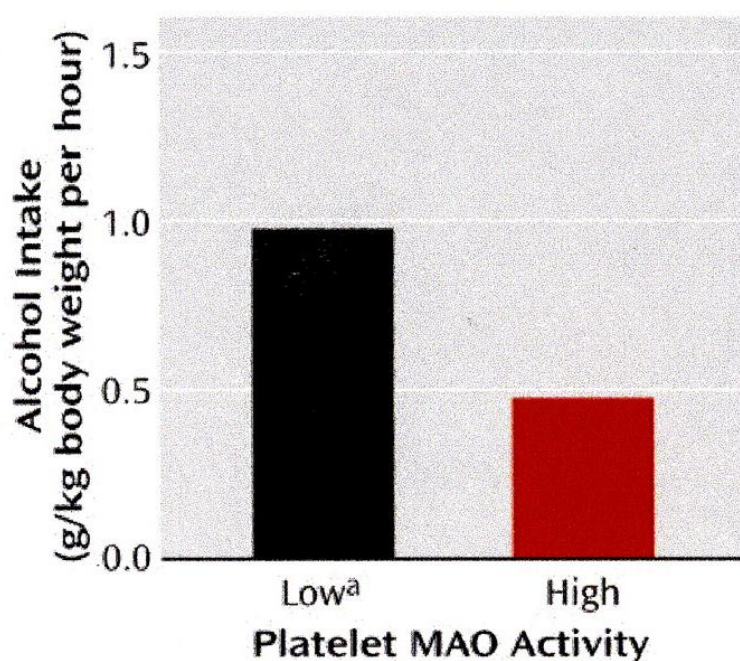
Heilig *et al.* 2011, 12: 670-684

# Alkoholi mõju võrdlevalt: akuutselt ja sõltuvuses



# Impulsiivsuskomponent

Vereliistakute-MAO, serotoniin ja alkoholi  
tarvitamine reesusmakaakidel



Fahlke *et al.*, *American Journal of Psychiatry* 2002; 159, 2107-2109



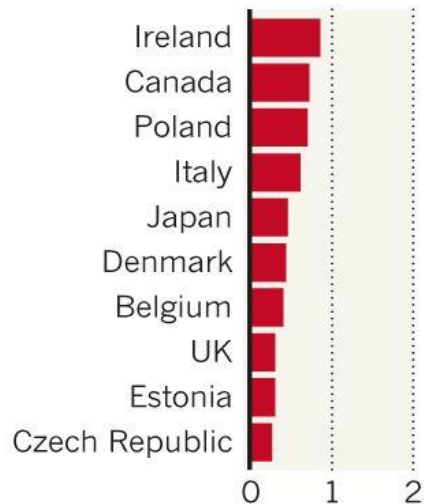


# Kliima soojenemine vähendab odrasaaki

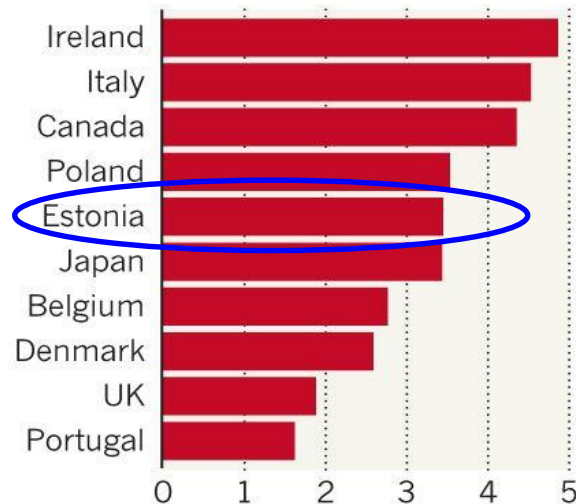
## CLIMATE'S TOLL ON BEER

Models show that during years of drought and heat waves driven by climate change, the global supply of barley — and therefore beer — will decrease and prices will rise.

Low-emissions scenario (RCP\*2.6)



High-emissions scenario (RCP8.5)



Changes in beer price (US\$ per 500 millilitres)

\*RCP, representative concentration pathway

©nature

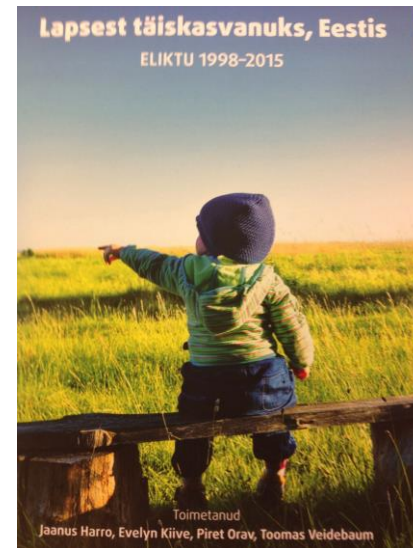
Võin teha panuse, et seegi mõjustab alkoholi kuritavitamise geneetikat

Figure: Warren Nature 15 October 2018; based on Xie *et al.*, *Nature Plants* 2018; 4, 964-973



# Infrastructure: the Estonian Children Personality Behaviour and Health Study (ECPBHS)

- Launched 1998; four data collection waves
- 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

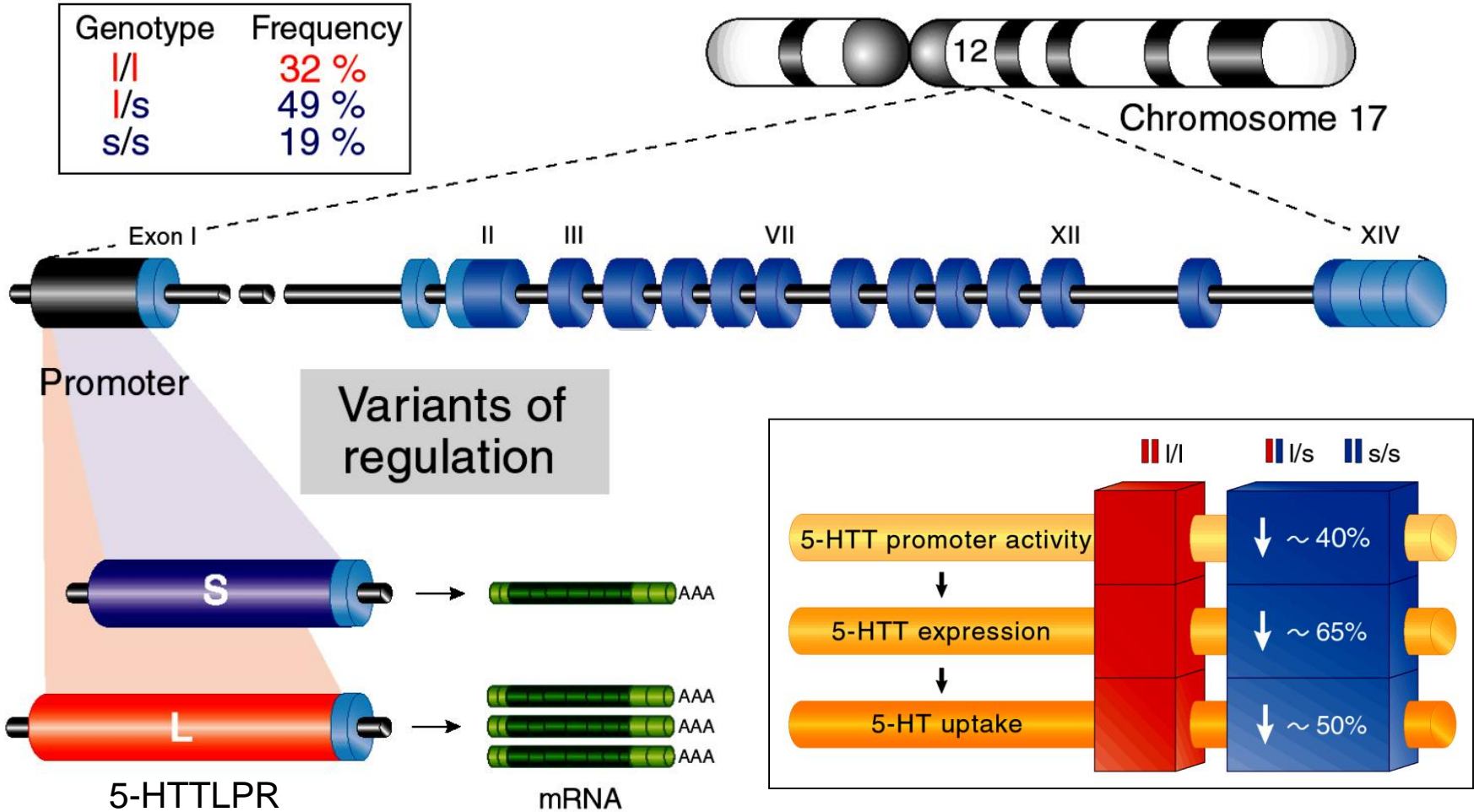




# Case Story: Variants of the Serotonin Transporter Gene



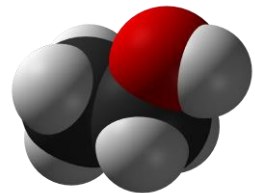
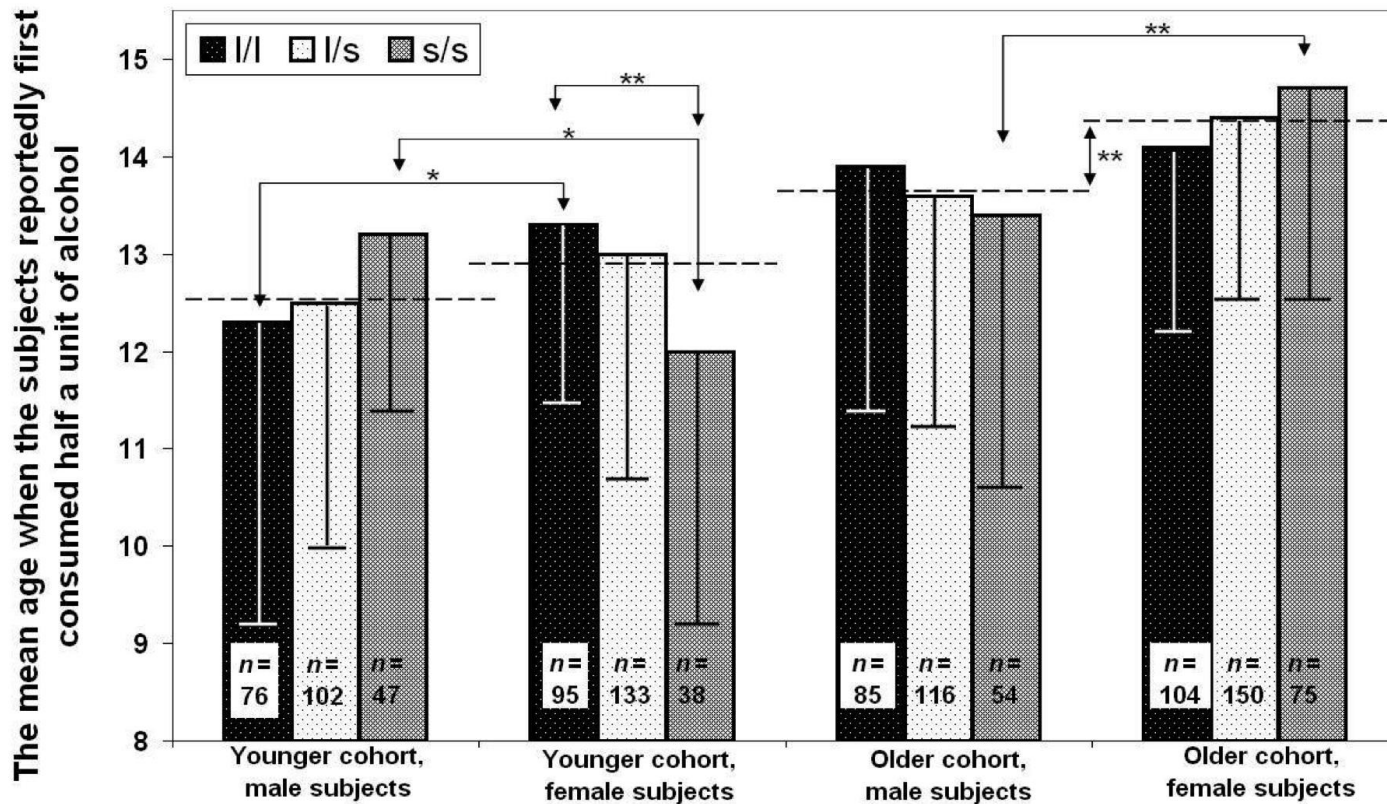
Lesch et al., Science 1996



Courtesy of Klaus-Peter Lesch



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



- Vaht *et al.*, *Psychopharmacology* 2014; 231, 2587-2594





Victoria, B. C. July 29 =

1885

No<sup>12</sup> Tai chung



Kwong On Lung & Co.

IMPORTERS AND WHOLESALE AND RETAIL DEALERS IN

Sugar, Rice, Tea, Opium, Groceries & Provisions

CHINA PROVISIONS.

Store Street, between Cormorant and Johnson.

Colonist Steam Presses.

		\$	¢
1885			
Feb.	13 Balance due as per ac rendered	2489	00
	19 Opium	100	00
	Salted turnips	18	00
	23 Opium	50	00
Mar.	4 China rice	525	00
	11 Opium	250	00
	17 Salted bamboo shoot.	48	00
	total	3436	88
Mar.	14 Received cash	500	00
	" charcoal	134	00
	Pork.	100	63
		734	63
	Balance due	2702	25
	Amount.		

Poeskäik 1885: suhkur, riis, tee, oopium, jmt kodukaup



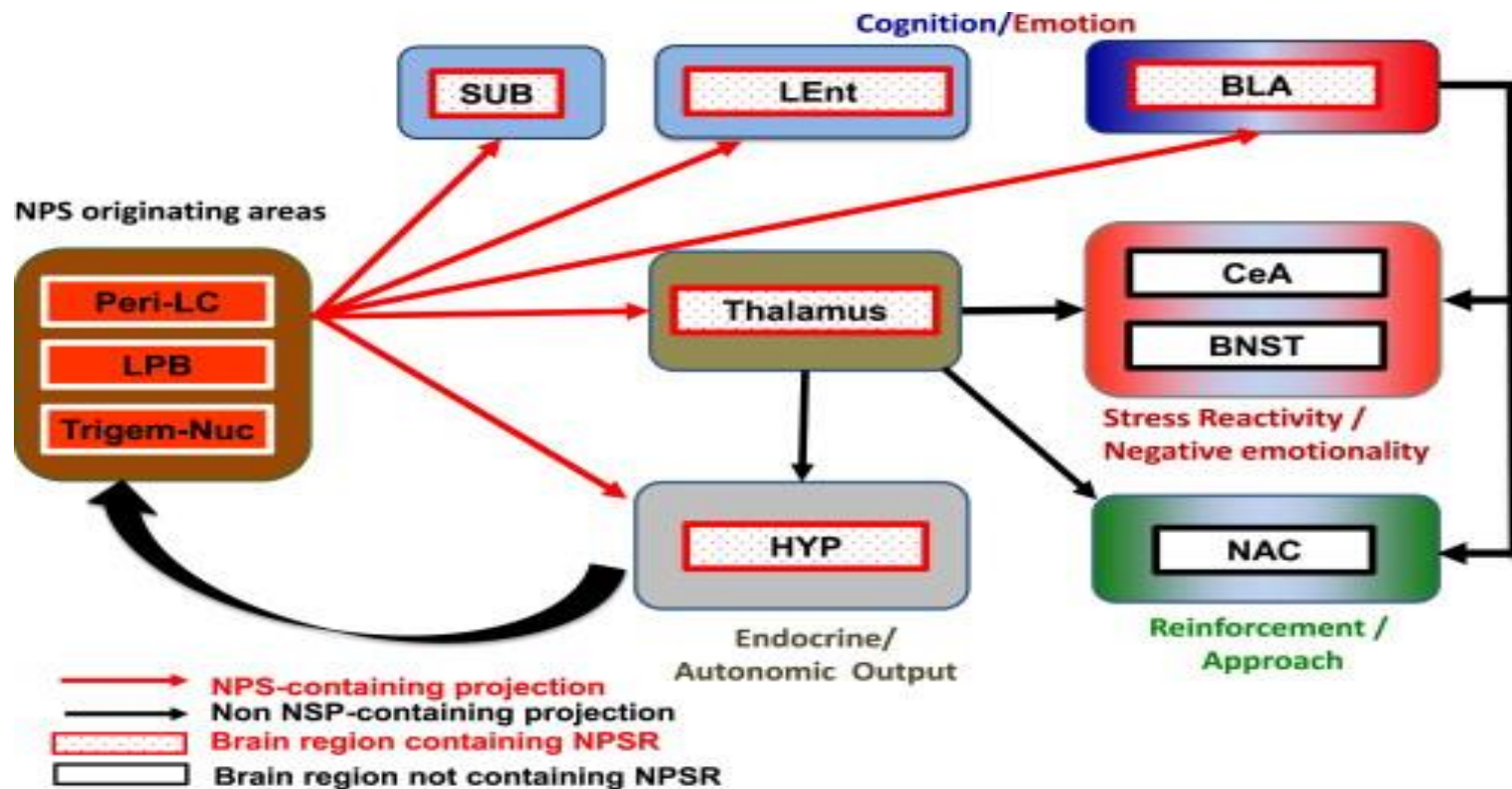
# Another case story: Neuropeptide S

- 20 amino acid peptide structurally similar in all mammals (Xu et al., 2004)
- Many NPS neurons also release glutamate or CRF
- NPS stimulates the HPA axis (Smith et al., 2006)
- Increase in wakefulness and decrease in both REM and non-REM sleep (Zhao et al., 2012)
- NPS effects mediated via a GPCR
- In rodents simultaneously activity-enhancing and anxiolytic (Xu et al., 2007; Ricci et al., 2008)
- Deficiency in NPS receptor in mice reduces locomotor activity and startle magnitude (Fendt et al., 2011)
- In humans, *NPSR1* at 7p14

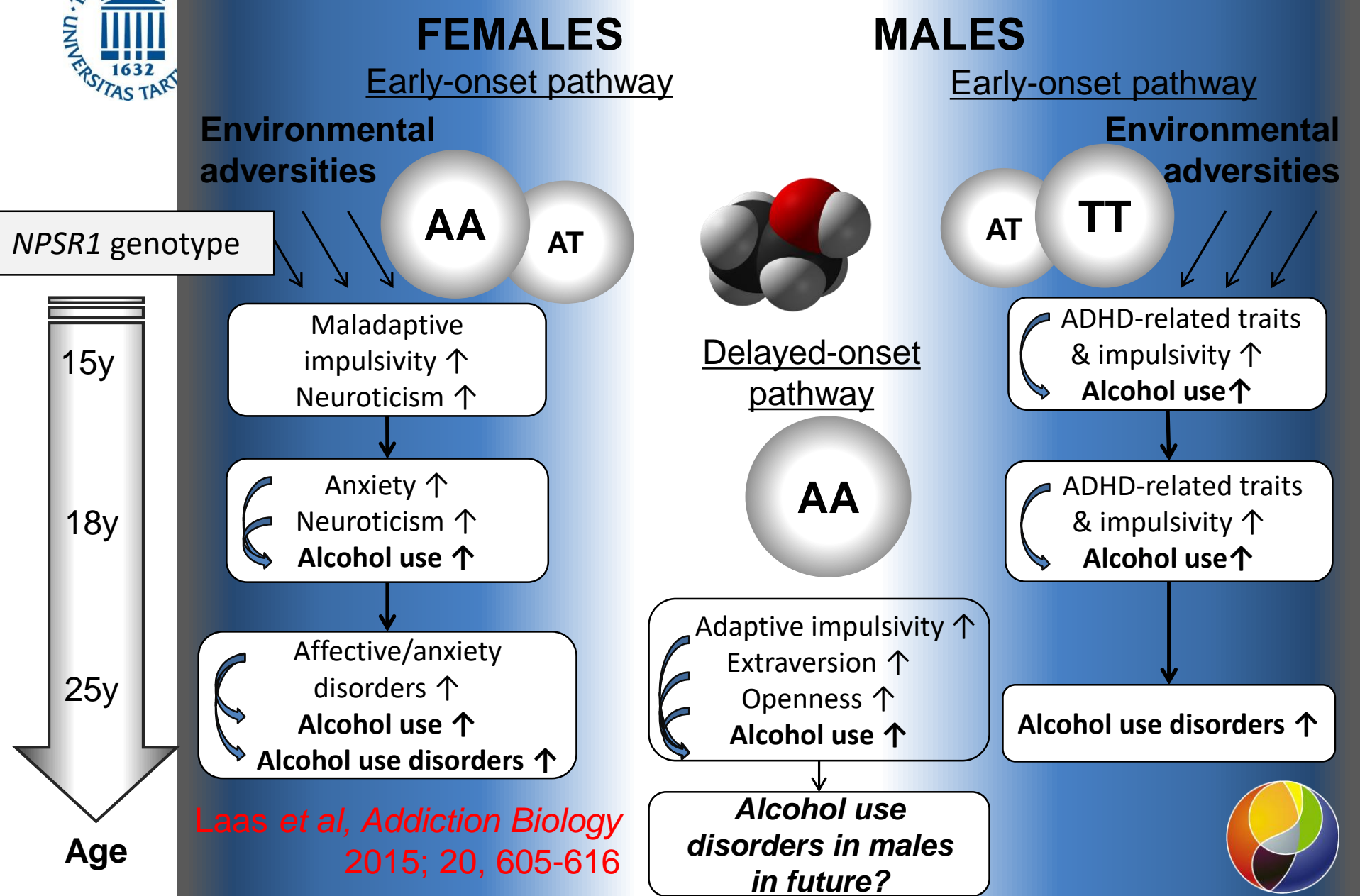




# Chemical neuroanatomy of neuropeptide S: relevance to alcohol



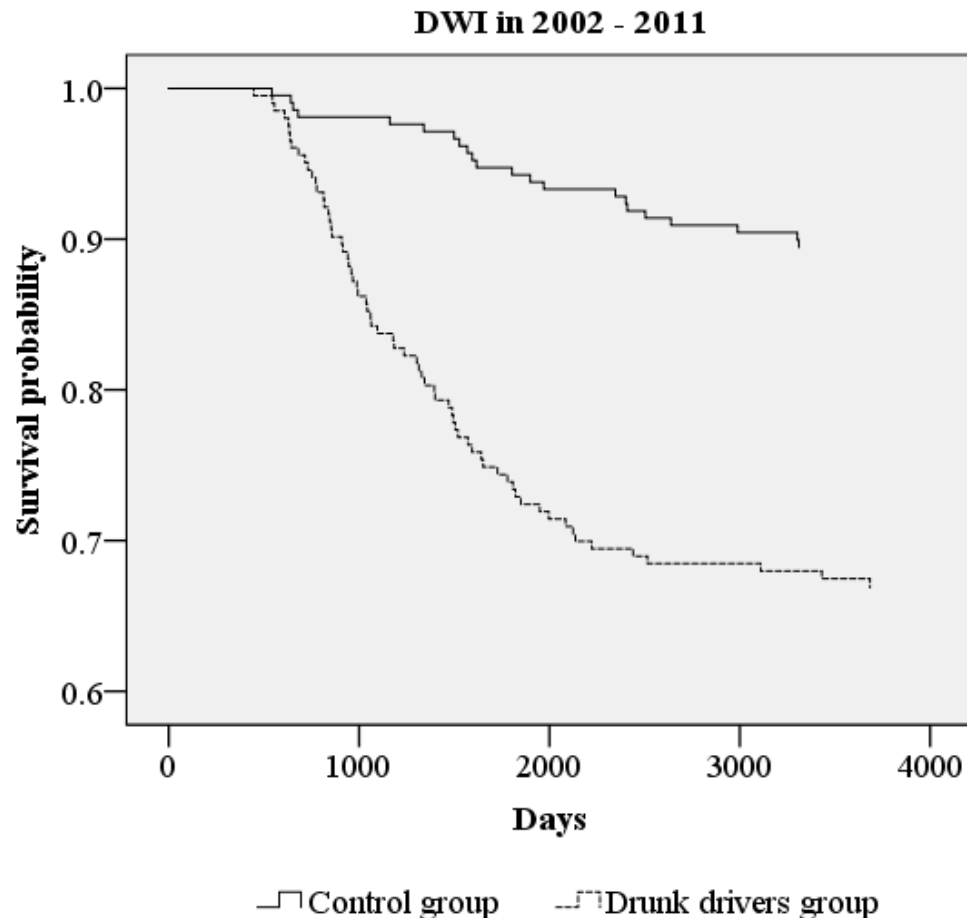
# Proposed pathways to AUD by *NPSR1*





# Follow-up of drunk drivers for the next ten years

- Traffic police database
- Cox regression models predicting drunk driving
- *NPSR1* T-allele vs. A/A homozygotes HR=1.76 (CI 1.02-3.03)
- But only with regard to relapse (i.e., in the initial drunk drivers group)





“If the environment changes, I change my mind. What do you do, Sir?” (John Keynes paraphrased by The Gene)

CHAPTER

2

c0002

Molecular Genetics Meets Sociology:  
Birth Cohort Effects on Alcohol  
Use and Relationship With Candidate Genes

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Division of Neuropsychopharmacology, Department of Psychology, Estonian Centre of Behavioural  
and Health Sciences, University of Tartu, Tartu, Estonia

In: Victor R. Preedy (Ed.), *Neuroscience of Alcohol: Mechanisms  
and Treatment*. Elsevier 2019; pp. 13-20





# Kokkuvõtteks

- Alkoholi ja aju kokkupuuted on sagedased
- Kasu-riski suhte hindamine käib paljudele üle jõu
- Kahjulik mõju kujuneb välja sammhaaval
- Sõltuvuse kujunemise otsustab ekspositsioon alkoholile
- Palju muutusi ajutalitluses ja virgatsainesüsteemides
- Geneetilised riskid on väga individuaalsed
- Käitumishäire patogeneesis mängib olulist rolli keskkond
- Geenide ja keskkonna koosmõjul on mitu iseseisvat rada
- Ka sõltuvusest vabanemine peab toimuma sammhaaval ja indiviidi arvestades

