# Alla- ja üleskäiguspiraalid süvaajus

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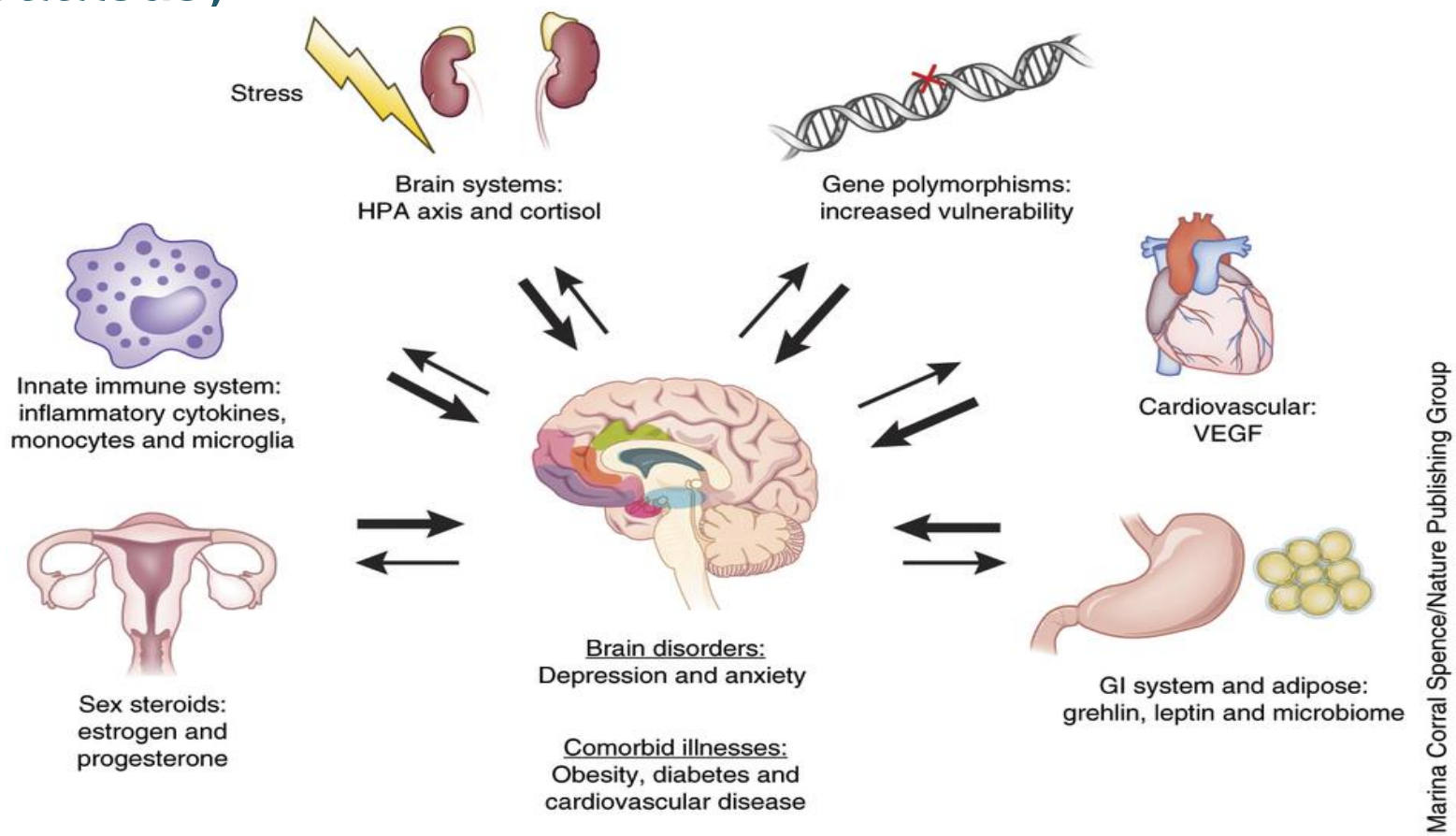
Tartu Ülikool
Põhja-Eesti Regionaalhaigla Psühhiaatriakliinik

"Kuhjuvale kurvameelsusele lahendusi otsimas"
Psühhiaatriakliiniku XI sügiskonverents, Hilton Tallinn Park, 23. november 2018

# Nähtamatu mõju ajule
## (kujutlege juurde nanoosakesed ja virtuaalne reaalsus)




Duman *et al.*, *Nature Medicine* 2016, 22: 238-249

**Kusjuures ainult veel hullemaks läheb …**

# Kliima soojenemine vähendab odrasaaki

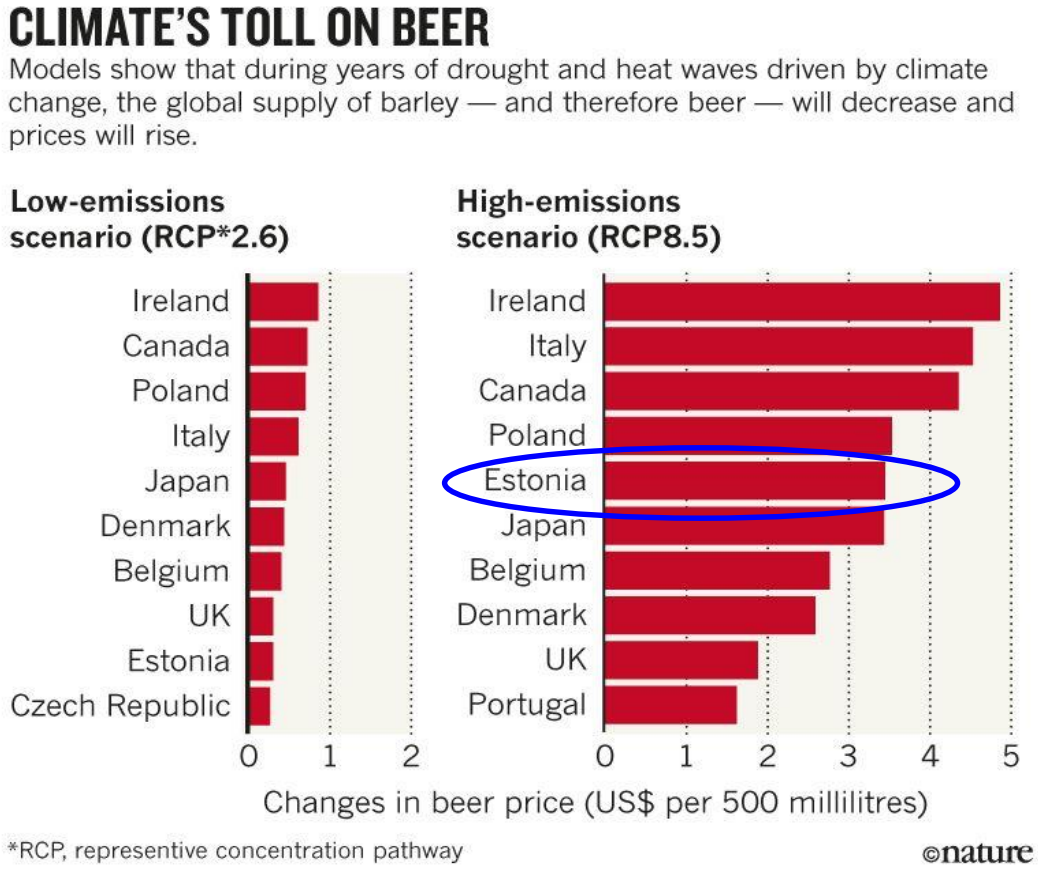
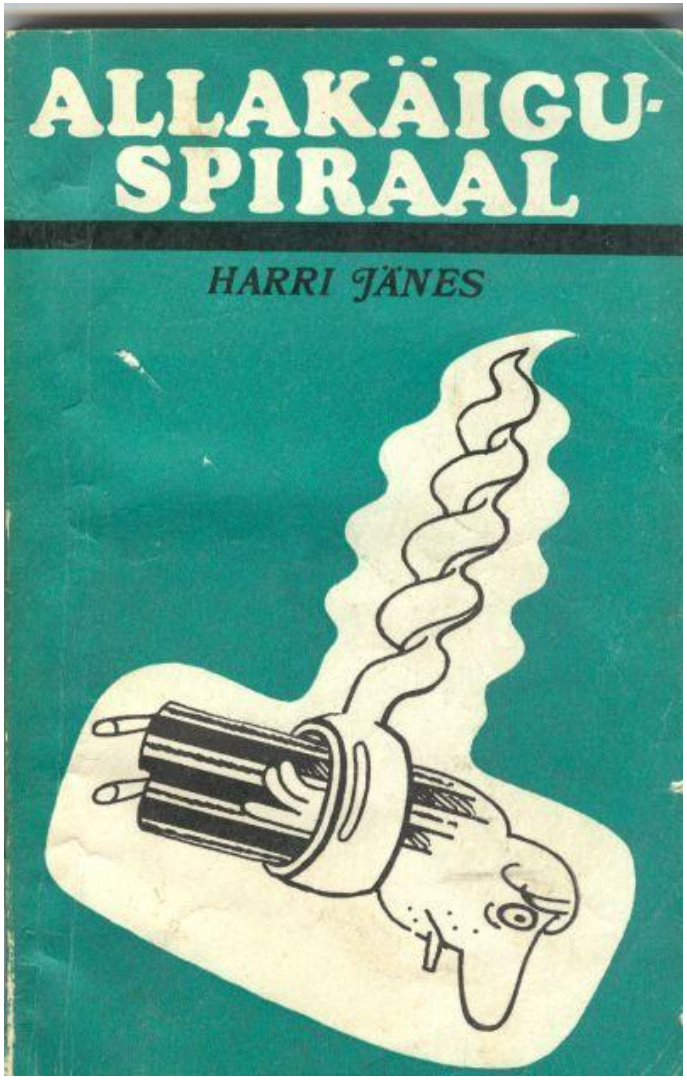



Figure: Warren *Nature* 15 October 2018; based on Xie *et al.*, *Nature Plants* (in press)

# Kuhjuv kurvameelsus ja allakäiguspiraal

- Kaasasündinud Achilleuse kannad, suuremad ja väiksemad
- Geenid,  ja siis ekspressioon
- Elukäigu algusest, looteeast peale
- Ja veel millises seltskonnas
- Mitte et kaugemal oleks parem
- Üha uued vastikud seltskonnad
- Pluss nanoosakesed ja mikroobid ja virtuaalsus
- Kuskil ei saa neist rahu
- Niimoodi inimest jääb järjest vähem

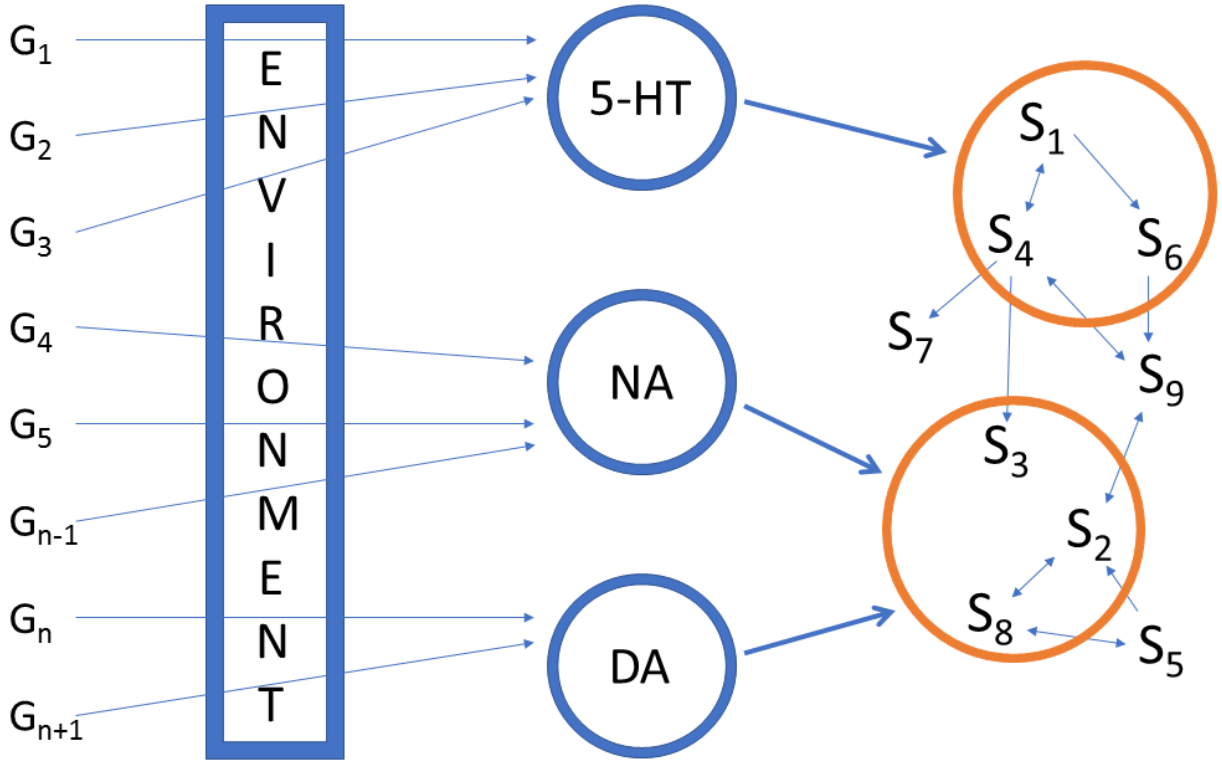


# Peamised üksteisest sõltumatud depressiooni riskitegurid

- naissugu (hmmmm…)
- distress varajases elus
- rasked üleelamised täiskasvanueas
- neurootilisus

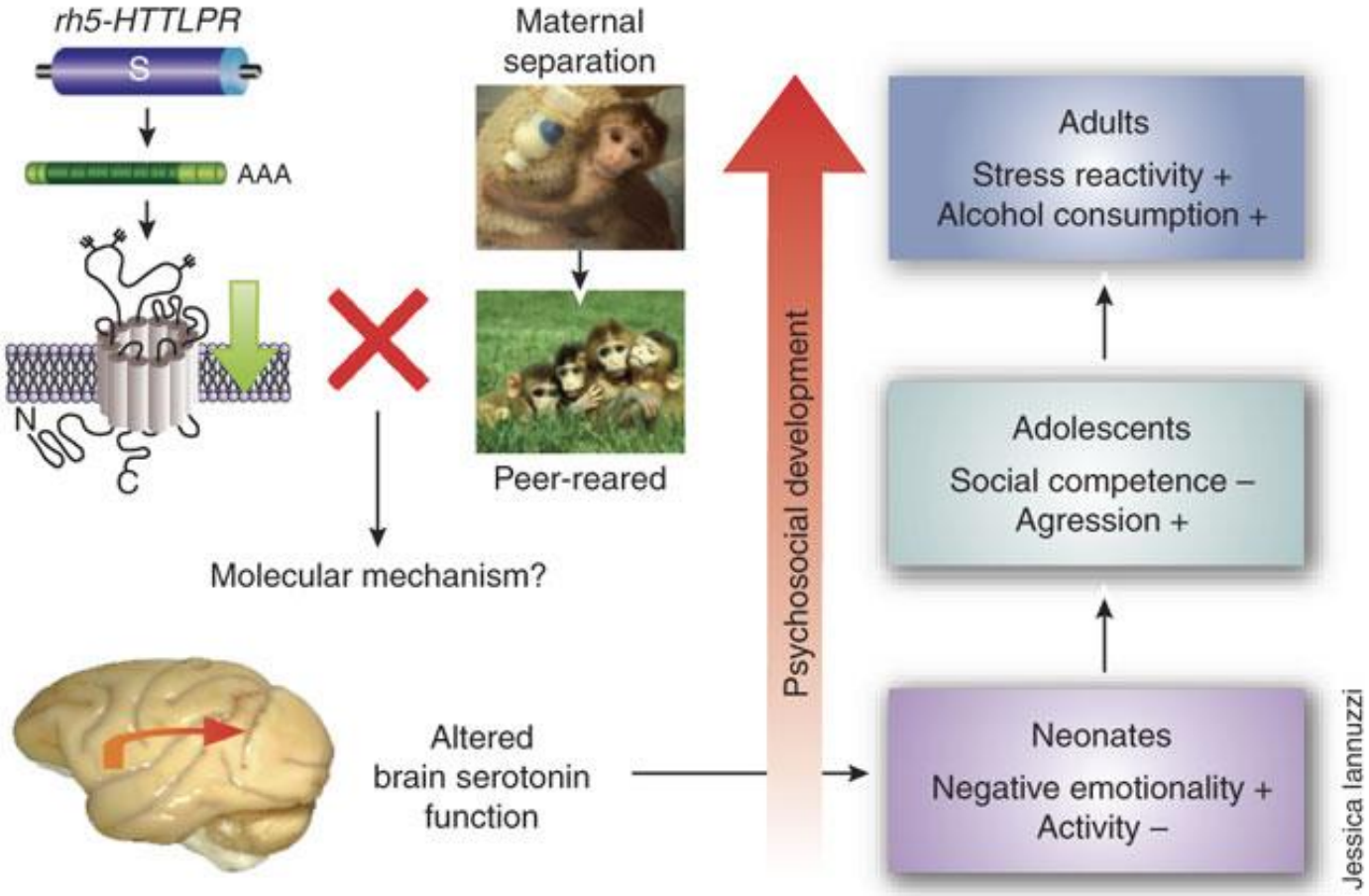
Fava & Kendler, *Neuron*, 2000; 28, 335-341

# Depressiooni väljakujunemine: läbi keskkonna



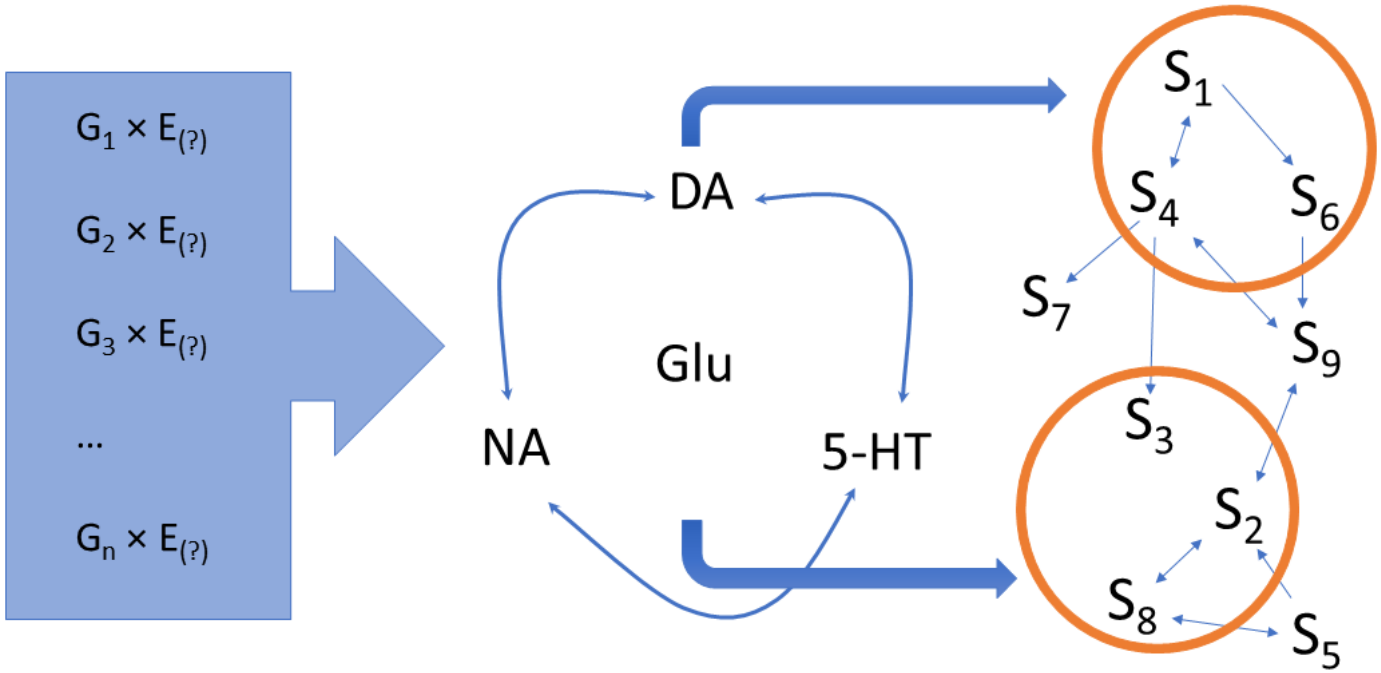

Harro, *Cell and Tissue Research*, resubmitted

# See kõik ei juhtu korraga: areng allakäiguspiraalil

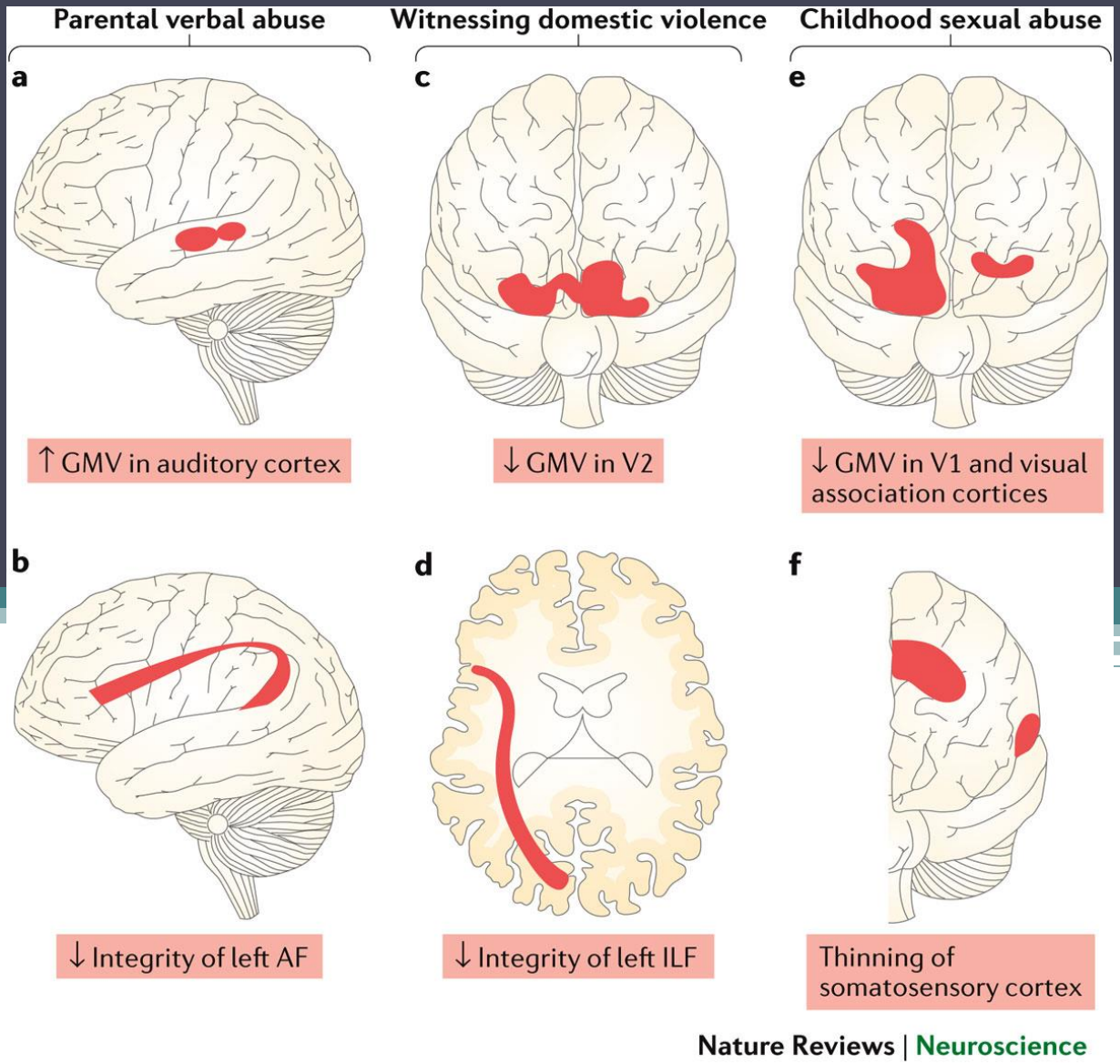



In rhesus macaques rh5-HTTLPR a similar genetic variance and similar vulnerability to humans

# *Circulus vitiosus* ja leviva korraldamatuse mudel

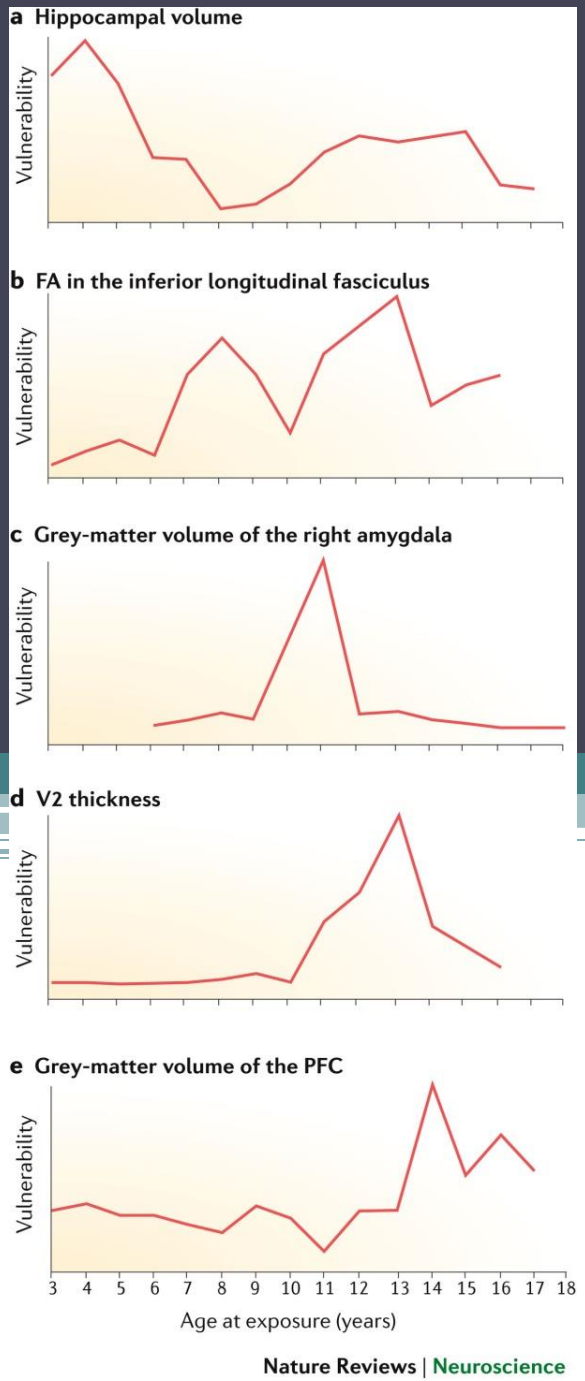



Harro & Oreland, *Brain Research Reviews* 2001, 38: 79-128;
Harro, *Cell and Tissue Research*, resubmitted

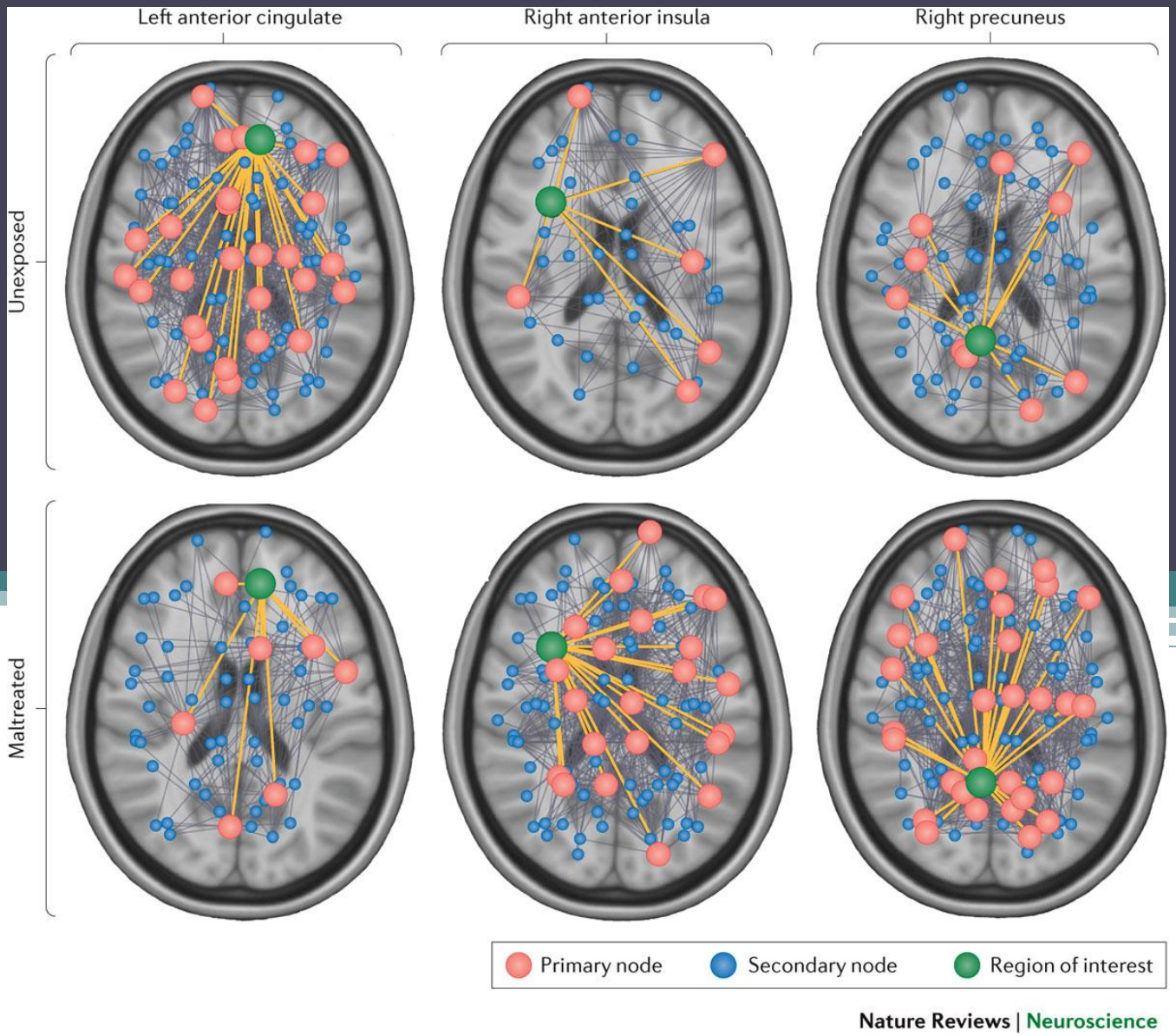



Teicher *et al.*, *Nature Reviews Neuroscience* 2016, 17: 652-666

# Iga asi omal ajal: haavatavuse eaaknad

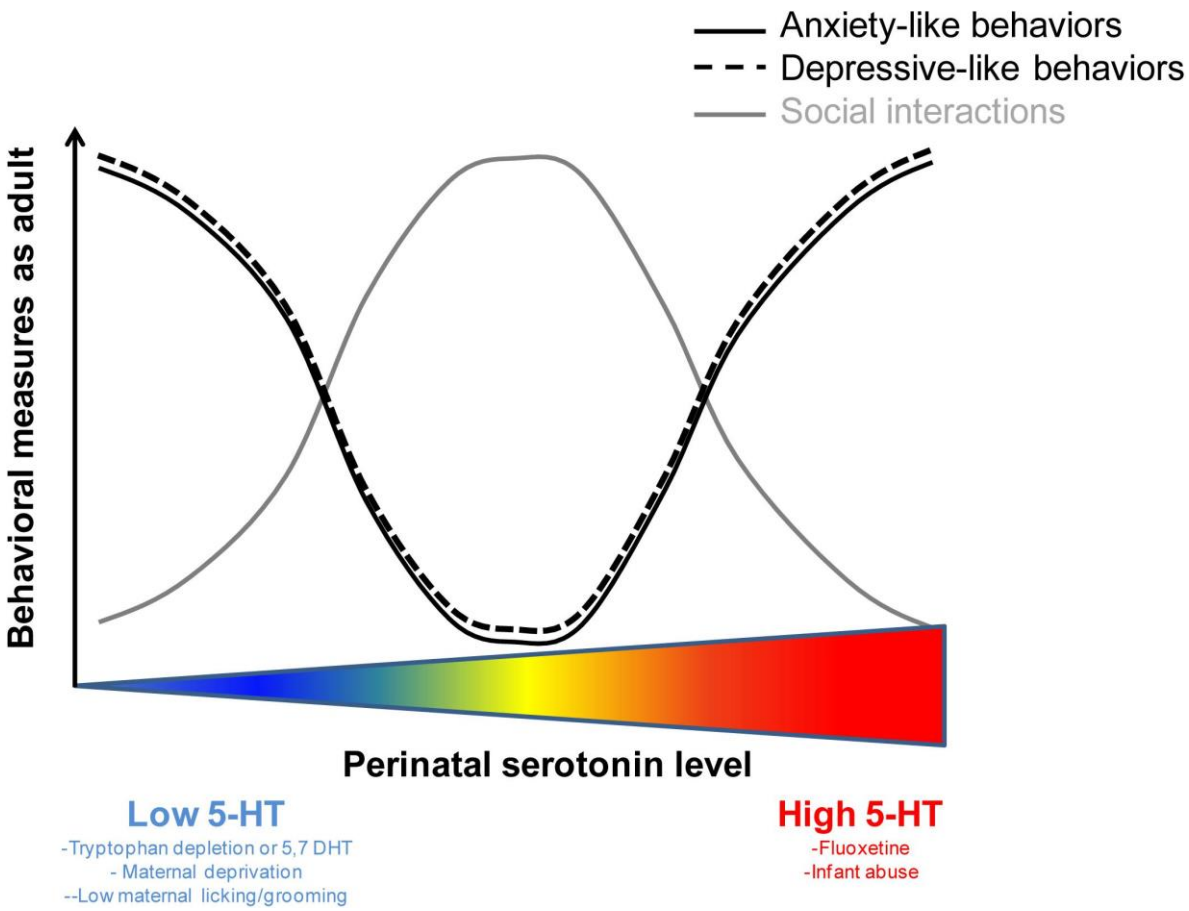



Teicher *et al.*, *Nature Reviews Neuroscience* 2016, 17: 652-666




Teicher *et al.*, *Nature Reviews Neuroscience* 2016, 17: 652-666

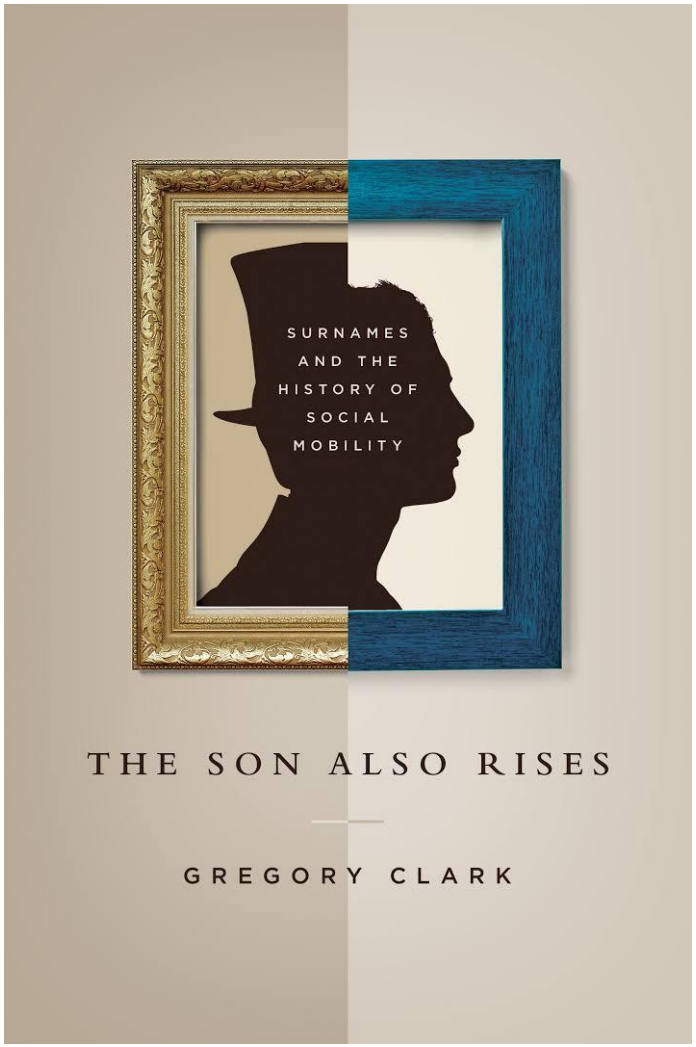
# Parasjagu serotoniini, juba varakult




Shah *et al., Frontiers in Behavioral Neuroscience* 2018; 12, 114

# Üleskäiguspiraalid?

- Sotsiaalne mobiilsus on piiratud
- Isegi kõige võrdsemates ja demokraatlikumates ühiskondades
- Selle tõestamiseks piisab ka kõige jämedakoelisemast sotsioloogiast – perenimede analüüsist
- **Vaimsele tervisele on see pelgalt peenhäälestus: süvaaju haarab igast õlekõrrest**

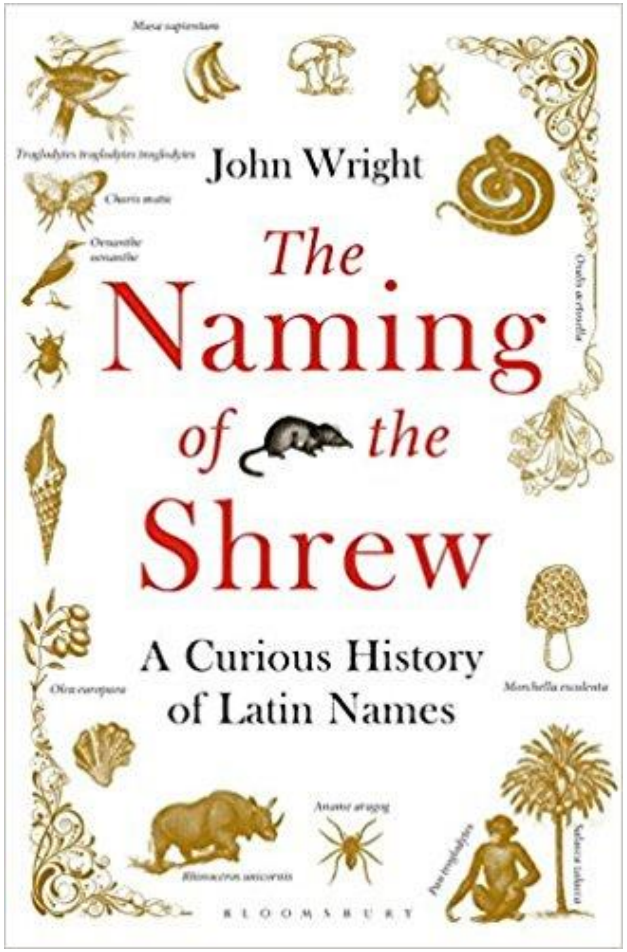


# Süvaaju?

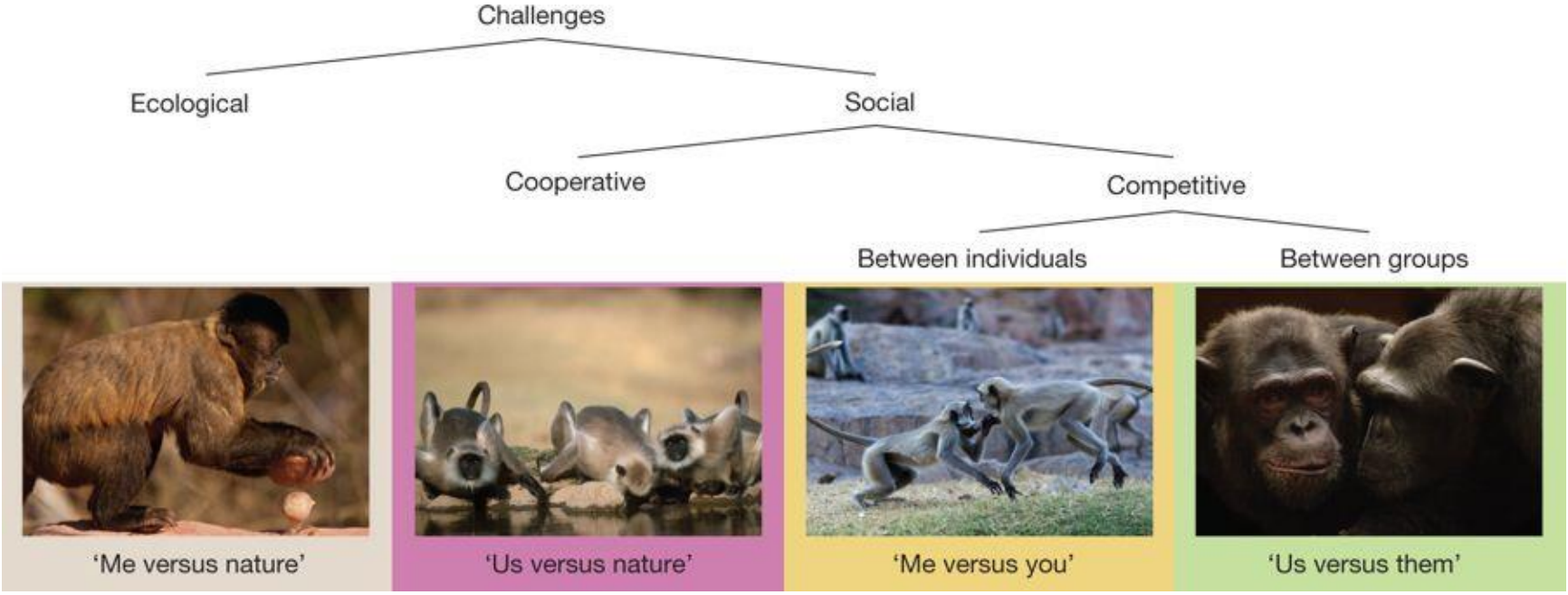
Hüsteeriline kangestus Esimese maailmasõja päevil (Val-de-Grace haigla muuseum Pariisis)

# “karihiirest rabatud”

- “shrewstruck” oli hiliskeskajal igati professionaalne diagnoos
- põhines ebausul, et karihiired on mürgised ja vanakurjaga ühenduses
- ja nii saidki inimesed halvatuse, mürgistuse, põletusi jm, kui tilluke karihiir nende kehast kusagilt üle jooksis



# Missugused jõud on kujundanud inimese energiakuluka aju?




60% 30% 0% 10%

- Kas see viib meid edasi, mis meid on siia toonud?

Joonis: González-Forero & Gardner, *Nature* 2018; 557, 554-557

- “Selliste mõistete nagu “soojätkamisinstinkt” või “enesealalhoiutung” selgitav väärtus on sama tühine kui oleks erilise “automobiilijõu” oma, mida ma võiksin sama õigustatult kasutada selgitamaks tõika, et mu vana hea auto ikka veel sõidab.”

Konrad Lorenz, *Das sogenannte Böse* (1963); e.k.
*Niinimetatud kurjus. TLÜ kirjastus 2017*

# Konrad Lorenz: neli suurt tungi

- toidu hankimine
- soo jätkamine
- põgenemine
- agressioon

Konrad Lorenz, *Das sogenannte Böse* (1963); e.k.
*Niinimetatud kurjus. TLÜ kirjastus 2017*

# Primaadil vähem kui küülikul, ja sügavamal

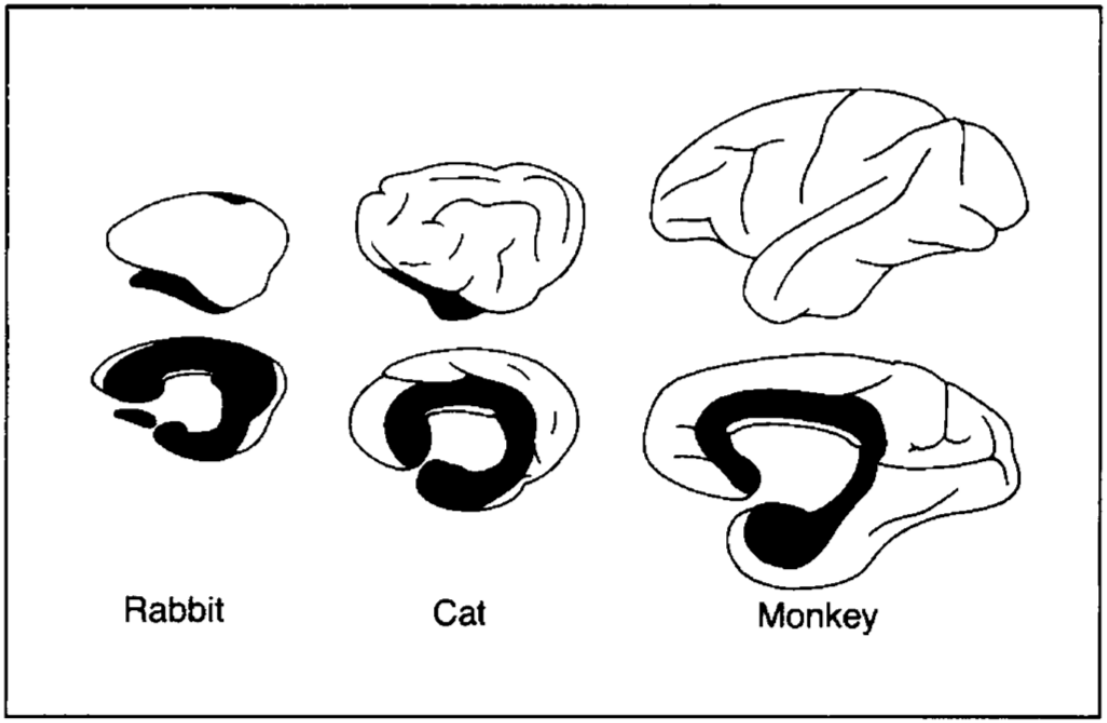



Fig 7.—Brains of three familiar animals, illustrating that great limbic lobe of Broca (shaded) exists as common denominator in brains of all mammals. Limbic cortex and associated structures of brainstem constitute limbic system, a derivative from early mammals (from MacLean[75]).

Picture: Paul D. MacLean, "Brain evolution relating to family, play, and the separation call." *Archives of General Psychiatry* 1985; 42, 405-417

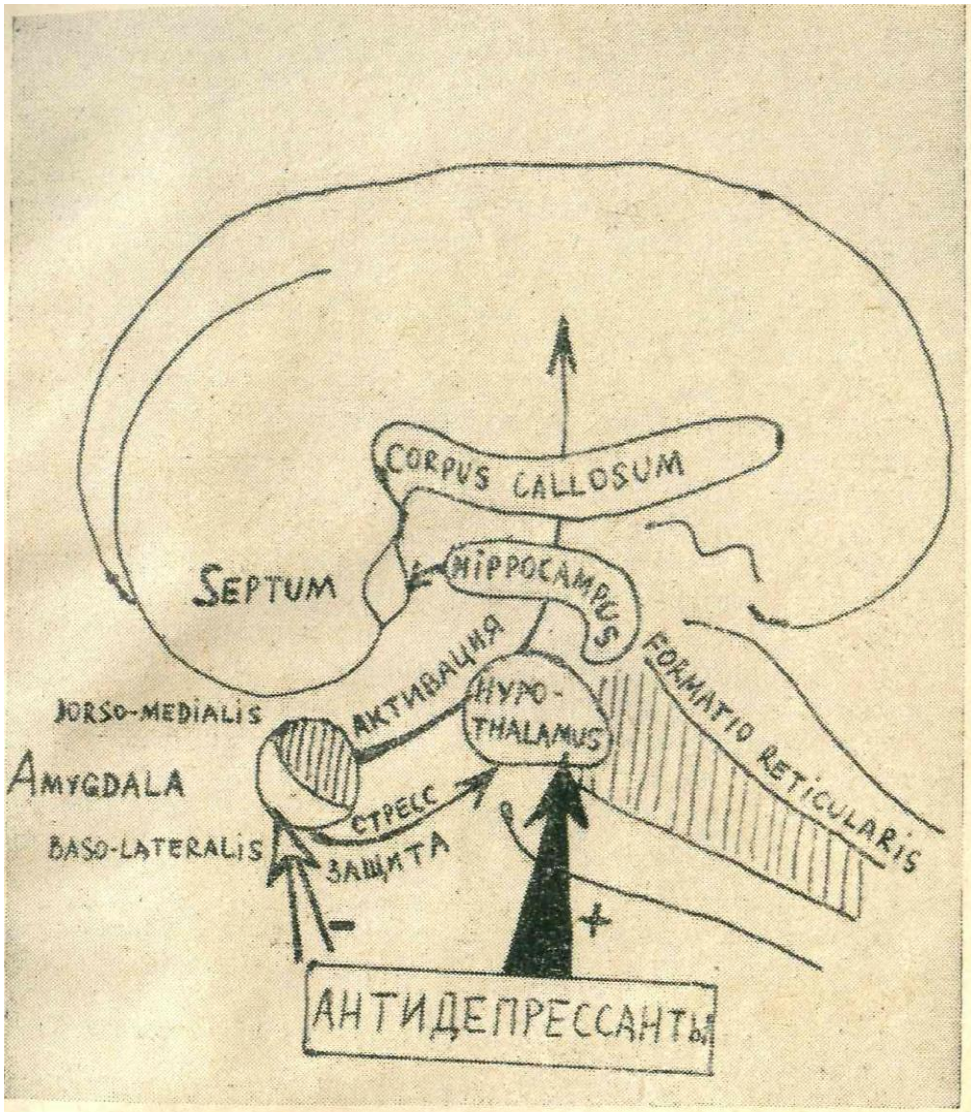
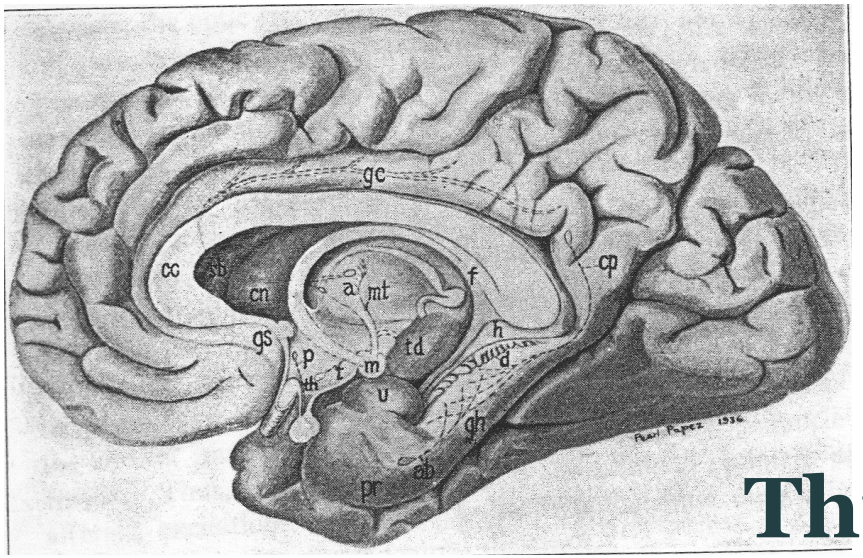
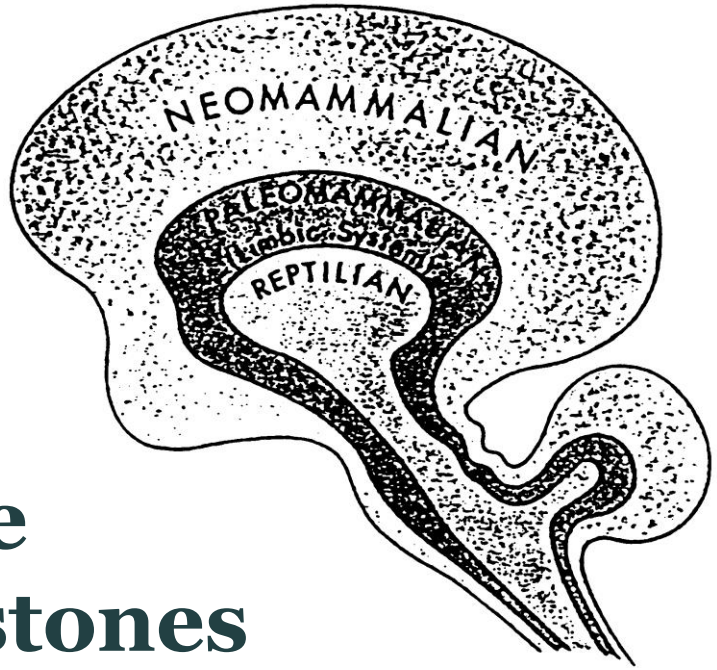



Схема локализации действия антидепрессантов группы имипрамина в глубоких структурах мозга.

# Üks varajasi katseid süvaaju mõista

Lapin & Allikmets, Leningrad 1967; 52, 19-30




# Three Milestones

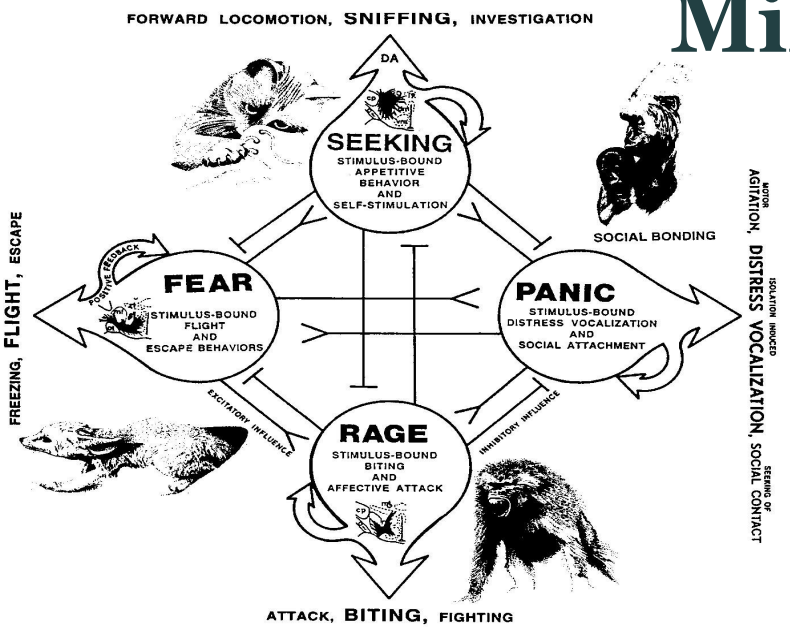



Fig. 3.5. AN

**James W. Papez** "A proposed mechanism of emotion." *Archives of Neurology and Psychiatry* 1937, 38: 725-743

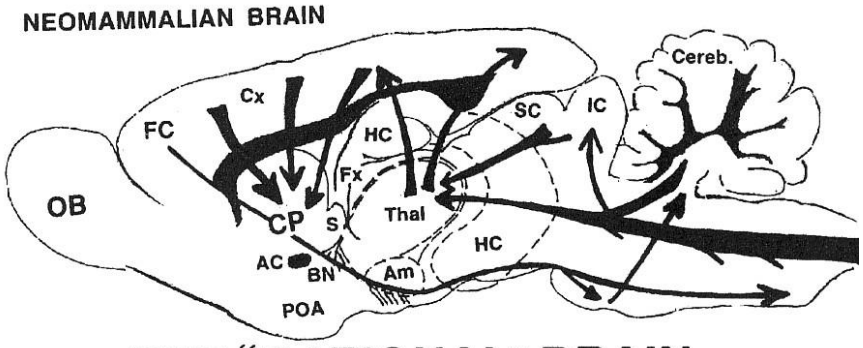
**Paul D. MacLean** *The Triune Brain in Evolution: Role in Paleocerebral Functions*. Plenum Press 1990

**Jaak Panksepp** *Affective Neuroscience, The Foundations of Human and Animal Emotions*. Oxford University Press 1998

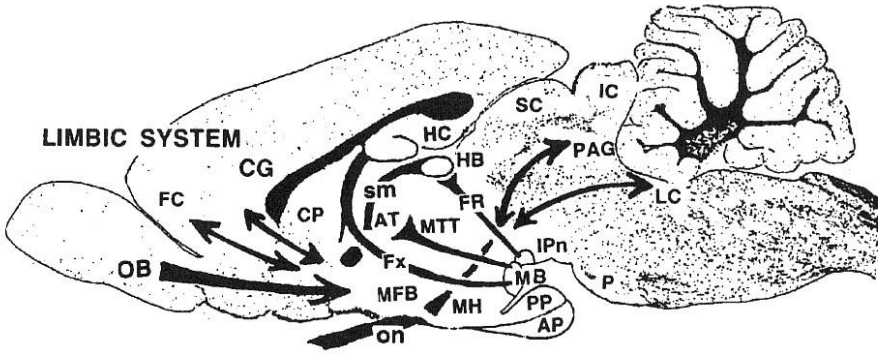
# The triune brain

- Ameerika arst ja aju-uurija, õppis Yale'i Ülikoolis, töötas Harvard'is, Yale'is ja *National Institute of Mental Health*'is
- "Vistseraalne aju", "limbiline süsteem" 1952
- *Emeritus*'eks suundumise aastal 1985 avaldas AGP-s artikli "Brain evolution relating to family, play, and the separation call." (1985; 42, 405-417)
- "Kolmetise aju" kontseptsiooni käsitlev raamat ilmus 1977 ja 1990

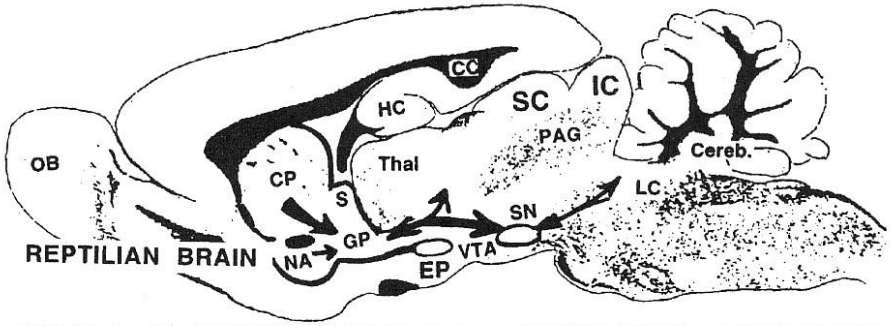
Paul D. MacLean (1913-2007)



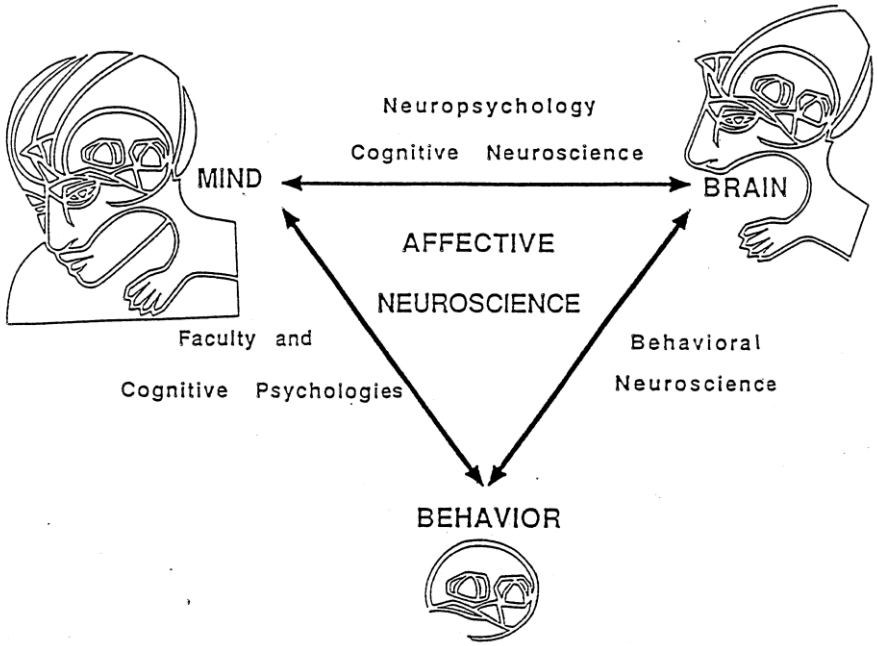

THE "RATIONAL" BRAIN




THE EMOTIONAL BRAIN



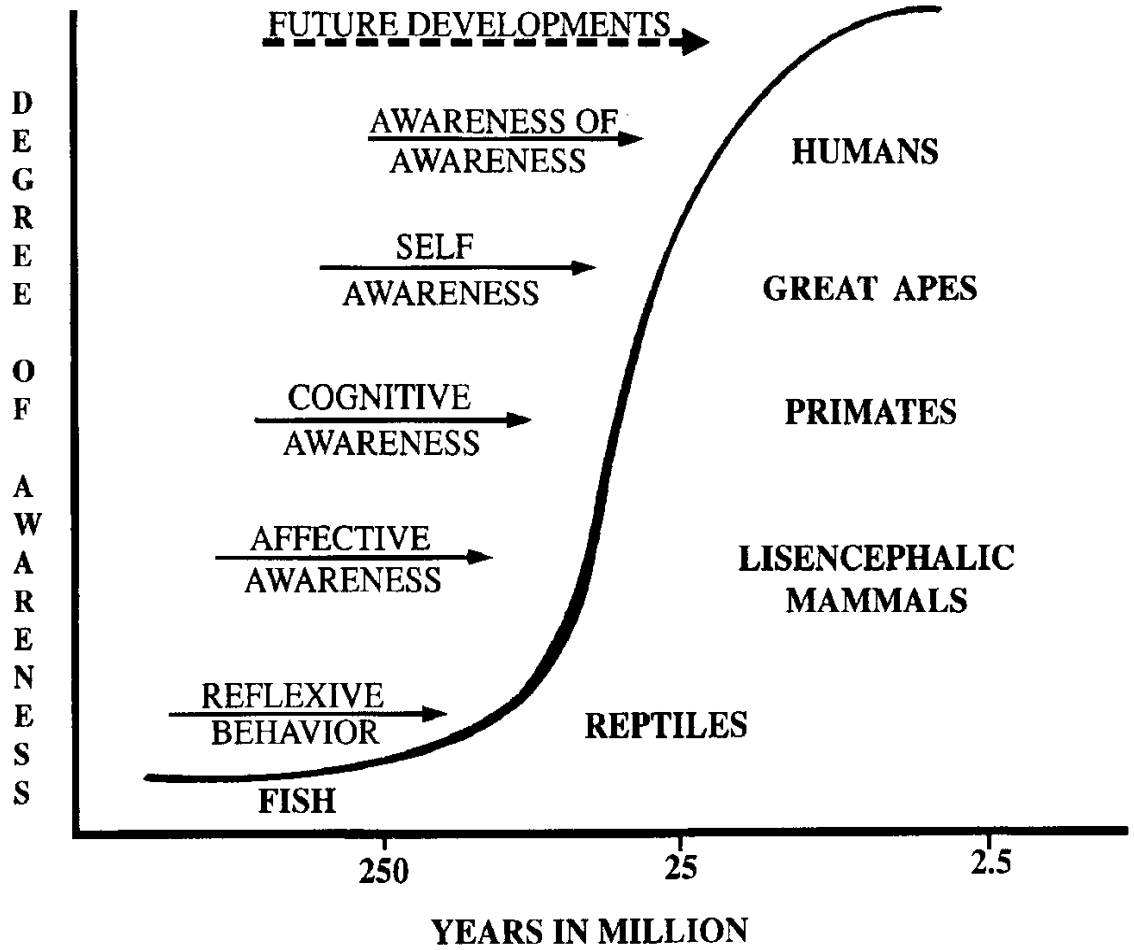

THE INSTINCTUAL MOTOR BRAIN




Kolmetine aju: uue imetaja, ürgimetaja ja reptiili "ajud" projitseeritult roti aju pikilõikele

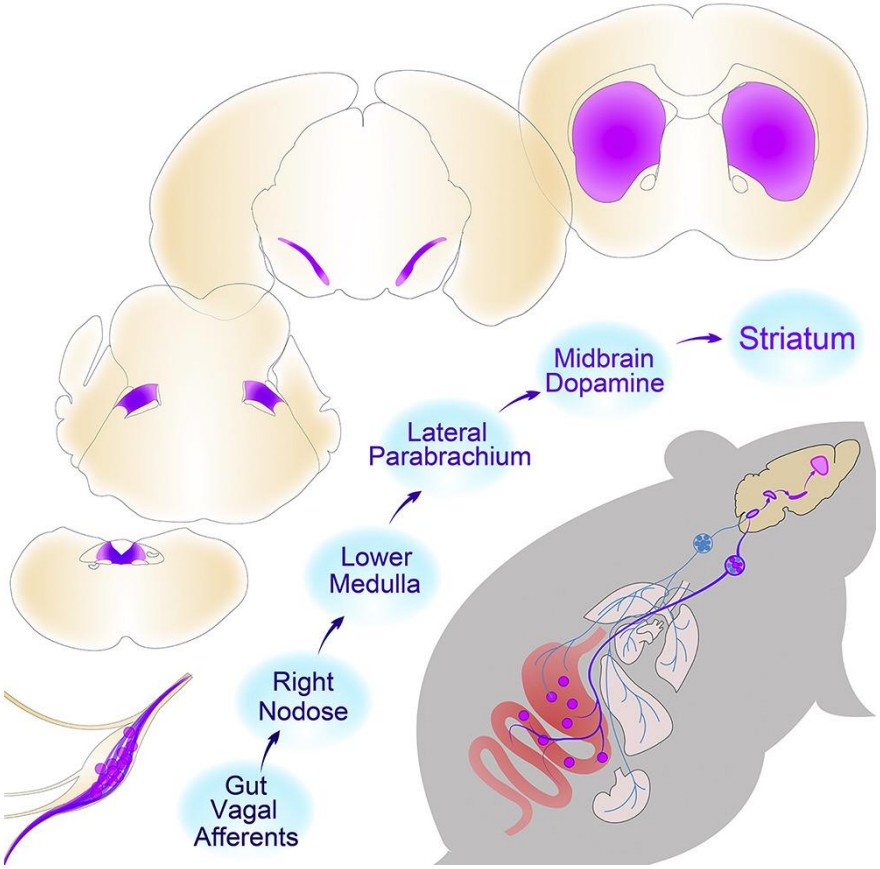
Jaak Panksepp, *Affective Neuroscience: The Foundations of Human and Animal Emotions*. Oxford University Press 1998

# Teadvelolek afektidest tekib koos imetajatetega

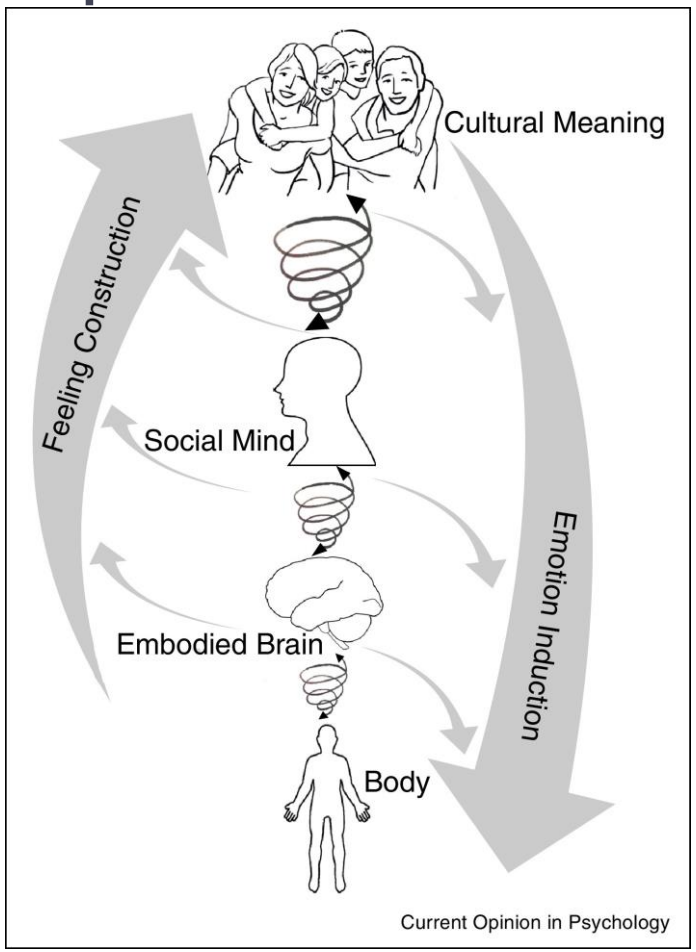



Jaak Panksepp, *Affective Neuroscience: The Foundations of Human and Animal Emotions*. Oxford University Press 1998

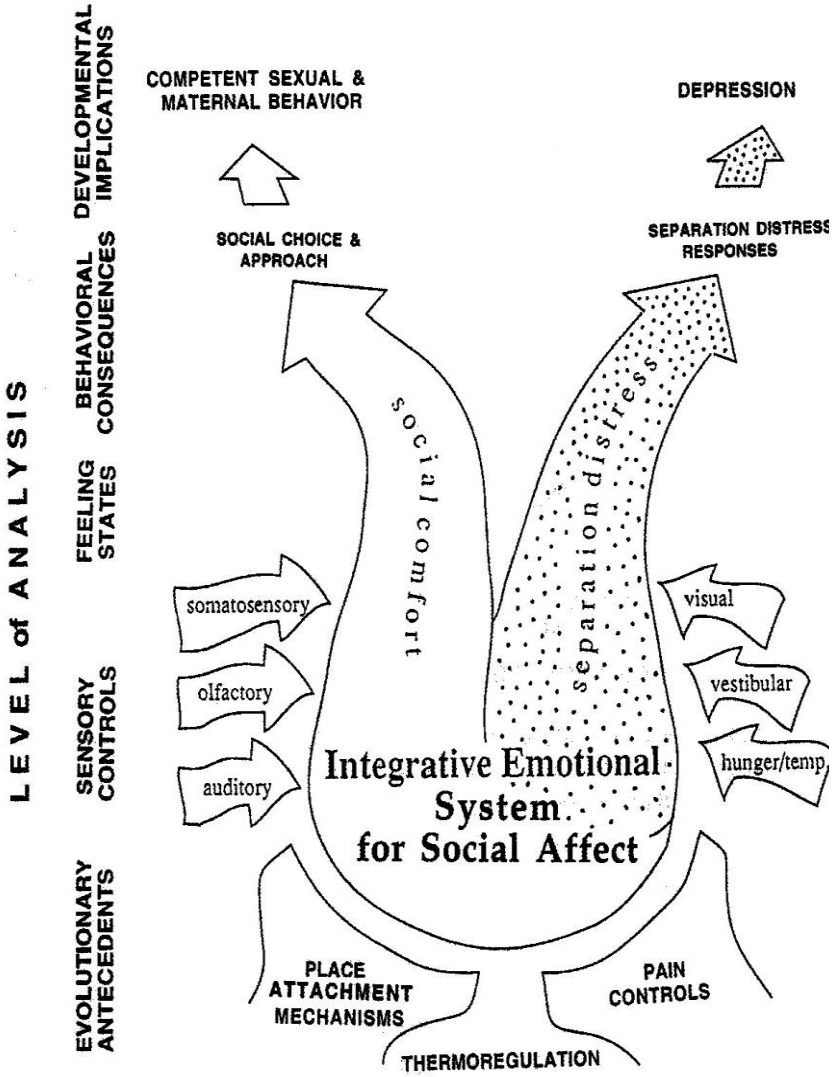
# Ajualused sõltuvad kultuurist, kuid kellel on kultuur, ärgu unustagu aju ... peensoolt ka

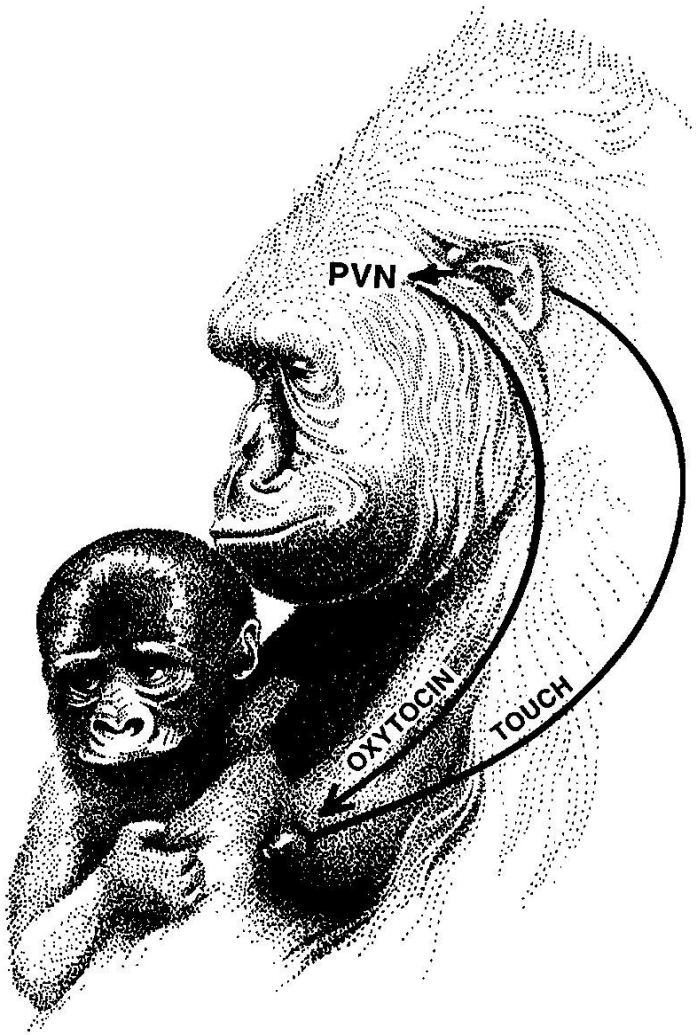



Han *et al., Cell* 2018; 175, 665-678




Immordino-Yang & Yang, *Current Opinion in Psychology* 2017; 17, 34-40




**Esimeseks vajaduseks on ohutu ja soe koht. Seejärel vesi ja toit.**

Fig. 14.1. AN

Fig. 13.3. AN

Jaak Panksepp, *Affective Neuroscience: The Foundations of Human and Animal Emotions*. Oxford University Press 1998

# Esimene psühholoog, kes kõdistas rotti

MEELIS A. PILLER

"Jah, mina kõdistasin neid rotte esimesena," naerab psühholoogiaprofessor **Jaak Panksepp** (55) Bowling Green State'i ülikoolist Ohiost (USA).

Rohkem kui kahesaja teadusliku artikli autor Jaak Panksepp lahkus Eestist koos vanematega juba aasta vanuselt. Vanemad pärandasid talle väga hea eesti keele ja eestlasele omase tegutsemistahte.

Panksepp on mitmeosalise "Hüpotalamuse käsiraamatu" ning raamatu "Emotsioonid ja psühhopatoloogia" kaastoimetaja, sarja "Bioloogilise psühhiaatria edusammud" toimetaja jne.

Professori töö on tihedalt seotud autistlike laste probleemidega – ta annab vastava mittetulundusorganisatsiooni all välja kvartaliajakirja Lost & Found, mida saadetakse puuetega laste vanematele.

Ligi 30 aastat aju-uuringutega tegelenud Panksepp on oma praegused uuringud suunanud emotsionaalse käitumise neuroanatoomiliste ja neurokeemiliste mehhanismide analüüsile.

"Oleme töö käigus jälginud, kuidas noored loomad mängivad," räägib professor, "ning püüdnud aru saada, millised keemilised protsessid samal ajal ajus toimuvad." Sealt tuligi Panksepp mõttele vaadata, kuidas rotid reageerivad kõdistamisele.

"Nüüd umbes aasta tagasi kuulsimegi esimest korda neid hääli – "rottide naeru"," meenutab Panksepp.

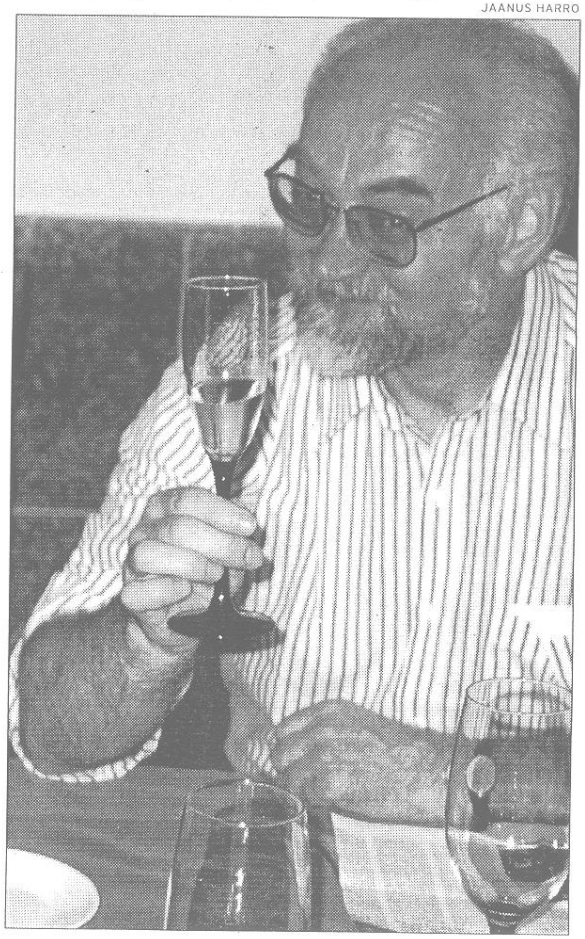
Katsetusteks võeti tavaline nahkhiire-detektor, mis võimaldab kuulata nahkhiirte poolt tekitatavat ultraheli. Rottide kõdistamisel edastaski detektor omalaadseid kilkeid sagedusel umbes 50 KHz – see on ligi viis korda kõrgem heli, kui inimkõrv on võimeline vastu võtma. Samad häälitsused kuulduvad ka noorte rottide müramise ajal. Põhimõtteliselt teati varemgi rottide kõrgsageduslikest häälitsustest, kuid seni seostati neid ainult ärituse ja armuhüüetega.

"Kõdistamine neile meeldib," märgib Panksepp.

Kuigi praegu neljaliikmeline uurimisrühm on tänaseks juba hulgaliselt materjali kogunud, pole põhjalikku artiklit tööst veel kirjutatud. Huvitavate tulemuste avalikustamine levis aga kulutulena üle maailma.

Nüüd me teame, et naer pole mitte ainult inimestele ja ahvidele omane reaktsioon – ka rotid võivad lõbusad olla.

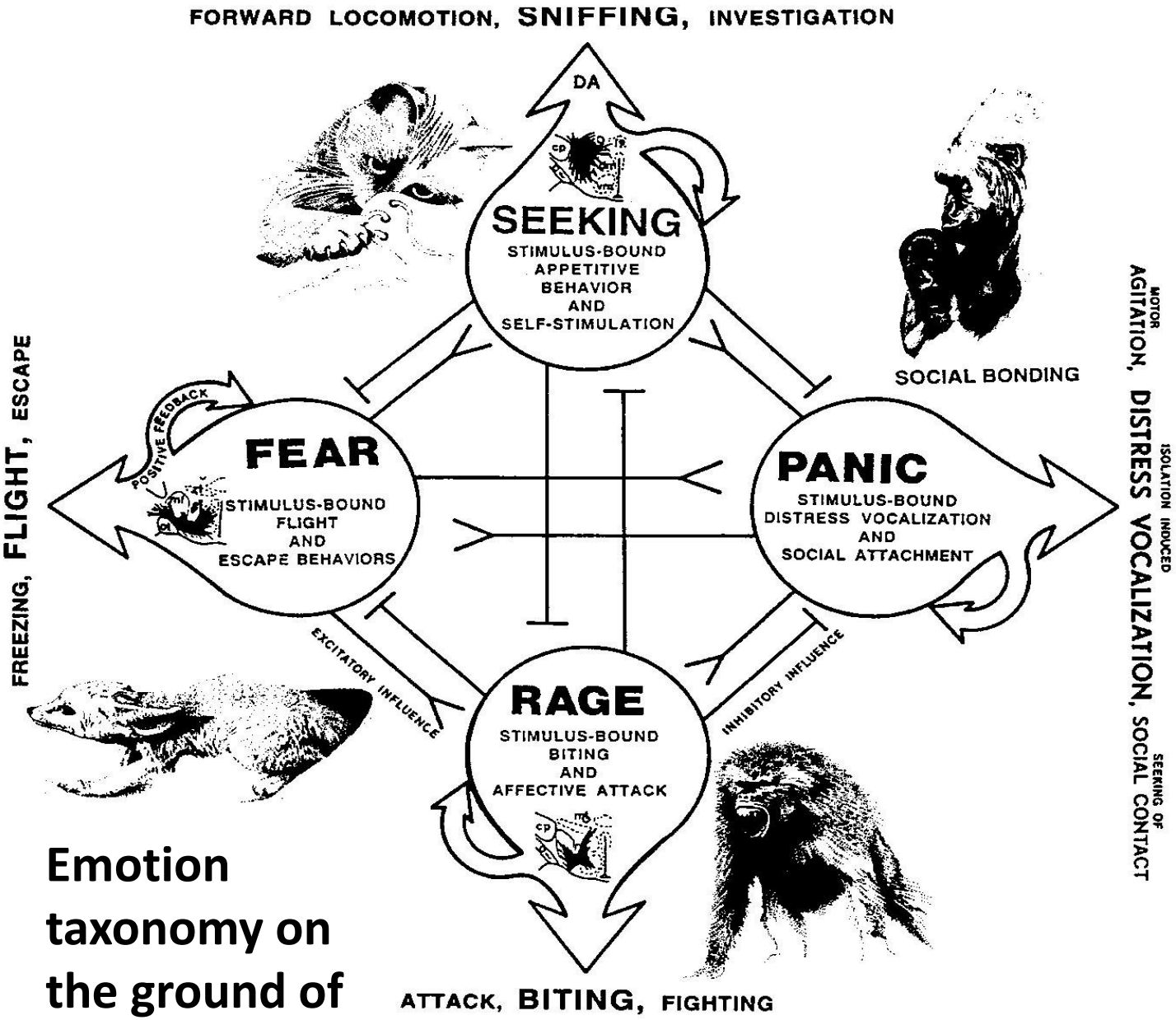
JAANUS HARRO



**MAAILMA TUNTUMAID EESTI SOOST PSÜHHOLOOGE: Aastakümneid aju uurinud professor Jaak Panksepp uurib praegu laborirottide reaktsiooni kõdistamisele.**

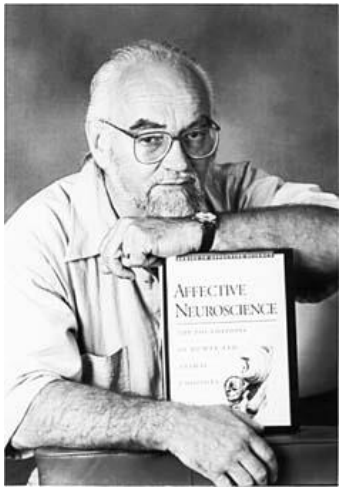
# Jaak Panksepp

## esimest korda Eesti ajakirjanduses



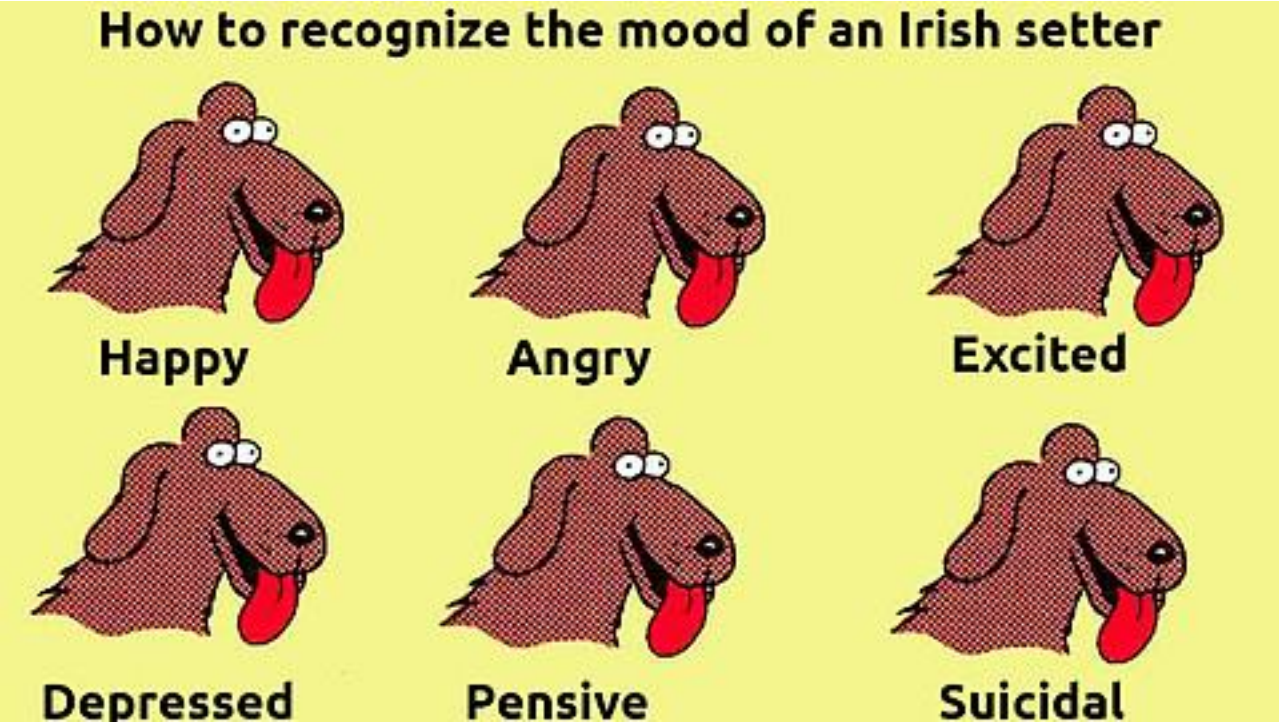

**Emotion taxonomy on the ground of cerebral circuits**

Fig. 3.5. AN



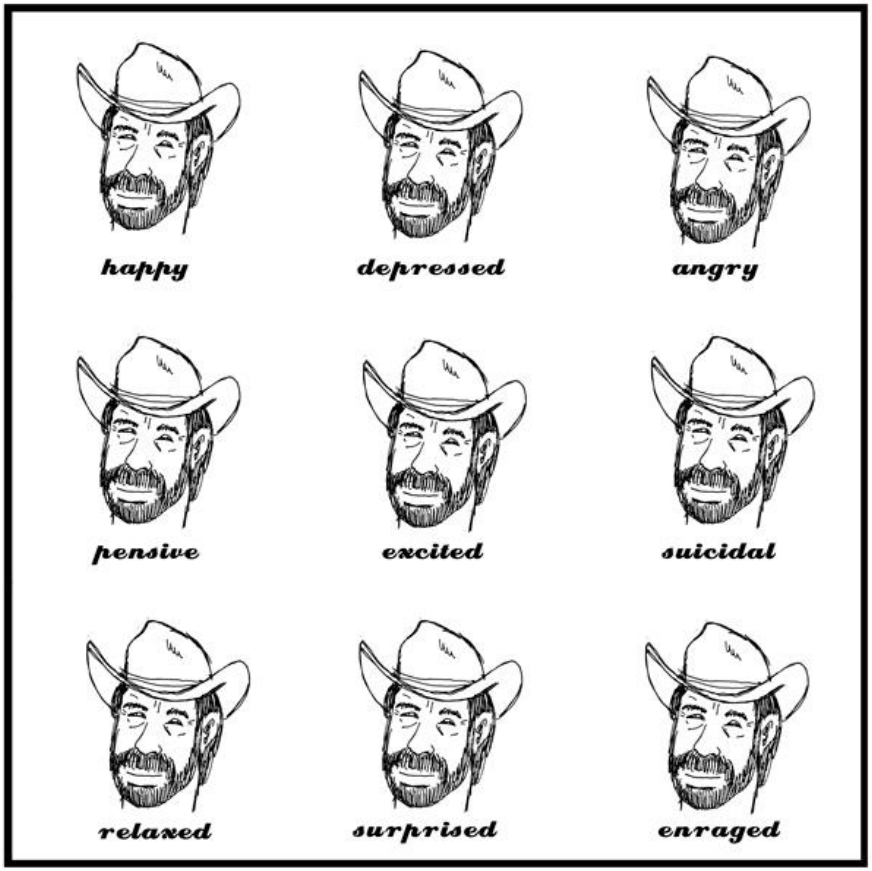

Modified from the 1982 BBS paper "Toward the psychobiological theory of emotion."

# Siiski, loomkatseid ei usu?




http://imgur.com/gallery/Rw81nPq

# Tõsi, ilme võib petta




- Emotsioon ei ole alati sõnastatav
- Kui on, ei ole alati seesama
- Ilme ja sõnad ei pruugi kokku käia
- Ja ega endalegi sellest täpselt aru ei anna

# Proovime häältega

- Hädahüüud siis, kui
  - üksi võõras kohas
  - üksi kodus

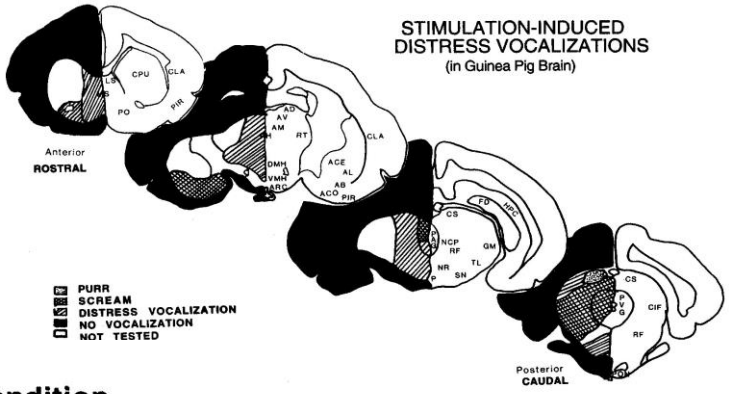



Fig. 14.4. AN

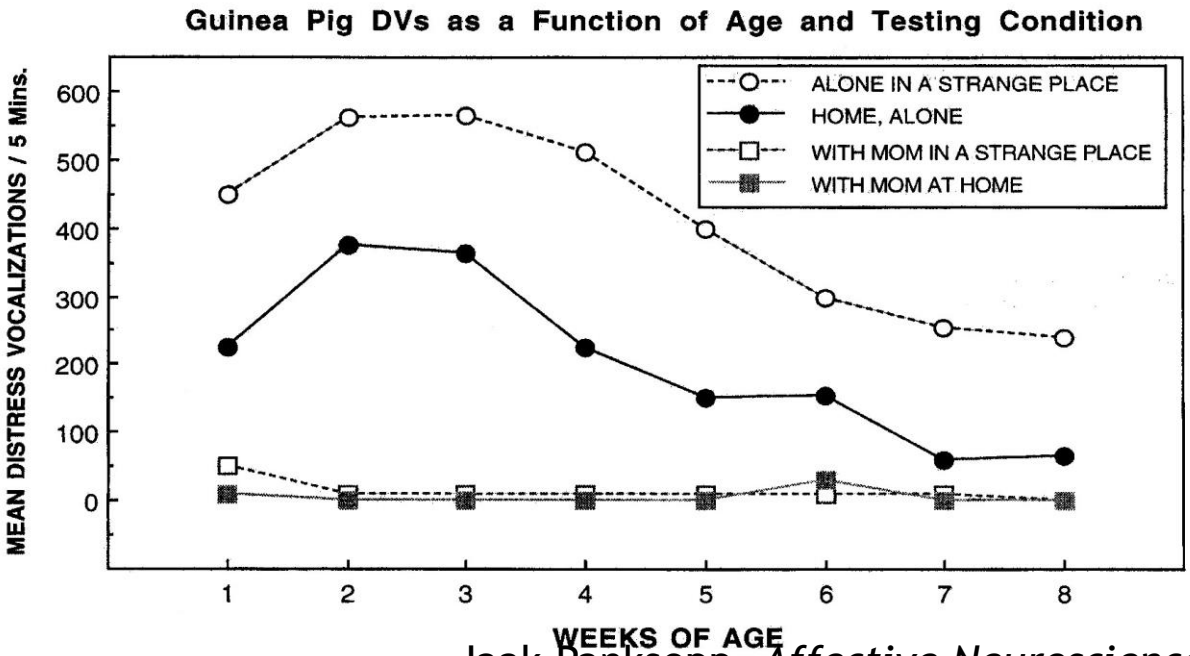
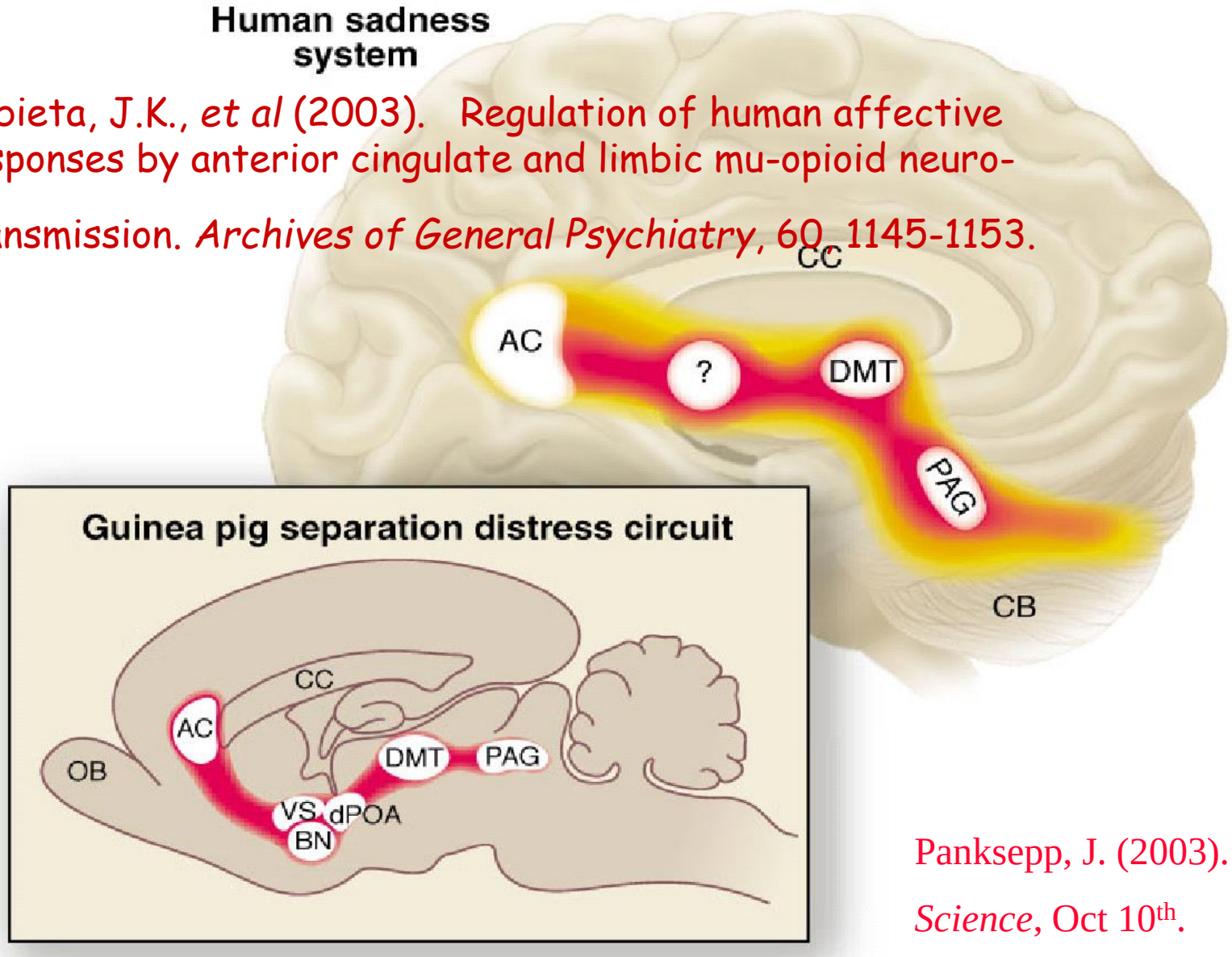



Fig. 14.3. AN

- Merisigadel, piirkonniti
  - nurrumine
  - kiljumine
  - hädahüüud

Jaak Panksepp, *Affective Neuroscience: The Foundations of Human and Animal Emotions*. Oxford University Press 1998

Zubieta, J.K., *et al* (2003). Regulation of human affective responses by anterior cingulate and limbic mu-opioid neuro-transmission. *Archives of General Psychiatry*, 60, 1145-1153.




Panksepp, J. (2003). *Science*, Oct 10th.

Panksepp 2004

| Basic Emotional Systems | Key Brain Areas | Key Neuromodulators |
|---|---|---|
| General Pos. Motivation **SEEKING**/ Expectancy ` System | Nucleus Accumbens - VTA<br>Mesolimbic and mesocortical outputs<br>Lateral hypothalamus - **PAG** | **DA (+),** glutamate (+), opioids (+), **neurotensin (+),** Many other neuropeptides. |
| **RAGE**/ Anger | Medial amygdala to Bed Nucleus of Stria Terminalis (BNST). medial and perifornical hypothalamic to **PAG** | **Substance P (+),** ACh (+) , glutamate (+) |
| **FEAR**/ Anxiety | Central & lateral amygdala to medial hypothalamus and dorsal **PAG** | Glutamate (+),**DBI, CRF, CCK, alpha-MSH, NPY** |
| **LUST**/ Sexuality | Cortico-medial amygdala,<br>Bed nucleus of stria terminalis (BNST)<br>Preoptic hypothalamus, VMH, **PAG** | Steroids (+), **vasopressin,** & **oxytocin, LH-RH, CCK.** |
| **CARE**/ Nurturance | Anterior cingulate, BNST<br>Preoptic Area, VTA, **PAG** | **oxytocin (+), prolactin (+)**<br>dopamine (+), **opioids (+/-)** |
| **PANIC**/ Separation | Anterior Cingulate,<br>BNST & Preoptic Area<br>Dorsomedial Thalamus, **PAG** | **opiods(-), oxytocin (-)**<br>**prolactin (-) CRF (+)**<br>glutamate (+) |
| **PLAY**/ Joy | Dorso-medial diencephalon<br>Parafascicular Area, **PAG** | **opioids (+/-),** glutamate (+)<br>ACh (+), TRH? |

# Kuidas siseneda üleskäiguspiraali?

“Kui üldse teie tekitate tolle (mis) teie sees, seesama mis on olemas teil, leeb päästmas teid, kui juhtub, (et) teil ei ole olemas toda (mis) teie sees, (siis) seesama mida ei ole olemas teil teie sees, /leeb sur/mamas teid.”

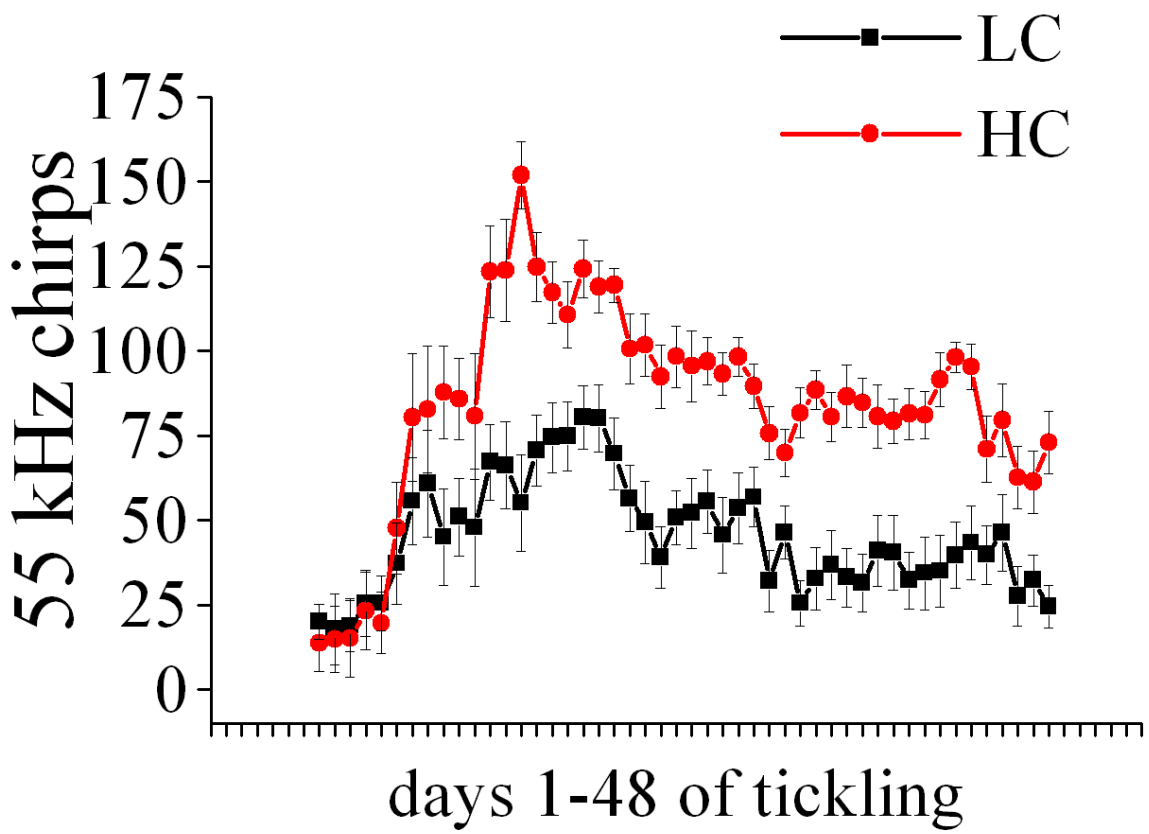
Tooma evangeelium
Uku Masingu tõlge
Johannes Esto Ühing 2005, lk 61-62

“If you bring forth what is within you, what you have will save you./--/ What you do not have within you will kill you.”

Gospel of Thomas


Teravad ja torkivad jäätmed
Avisoft ULTRASOUND

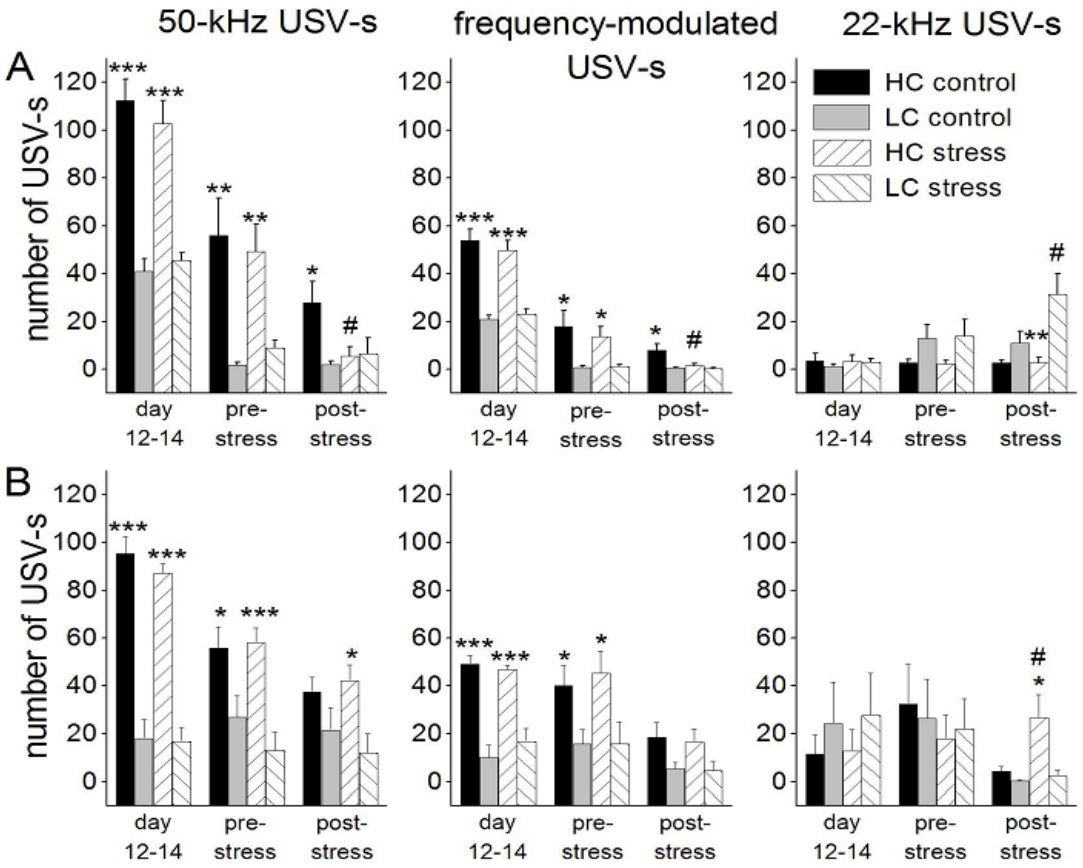
# Trait of experiencing positive emotions:
## rats with low vs high 50-kHz vocalization response




When given daily tickling sessions after weaning at age of 21 days, rats develop characteristic levels of responding with 50 kHz calls after two weeks of treatment. This response does not correlate with the expression of 22 kHz distress vocalizations (Mällo *et al, Behav Brain Res*, 2007, 184: 57-71)

HOPE FOR DEPRESSION
RESEARCH FOUNDATION

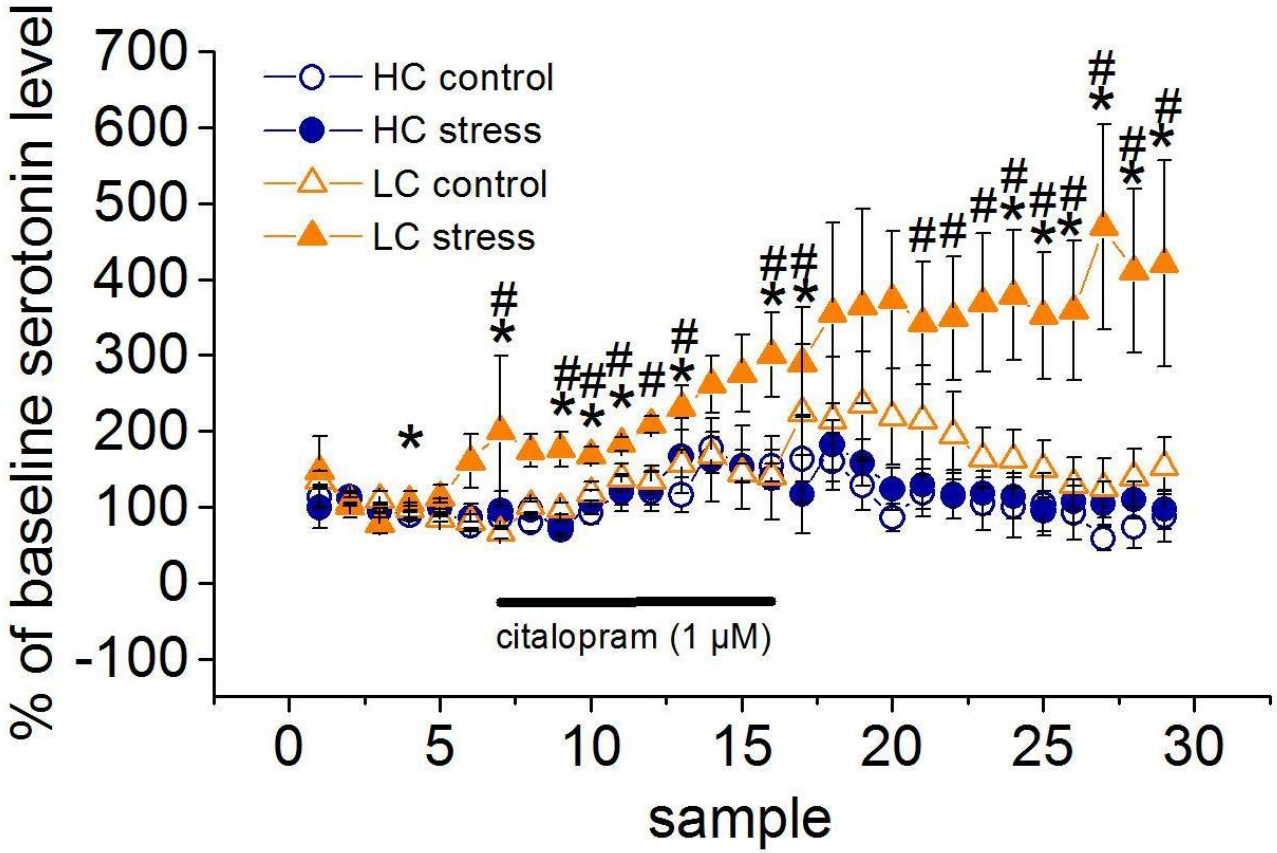
# Positiivne afektiivsus kaitseb stressi eest




- Stress vähendab 50-kHz häälitsusi
- Stress rohkendab 22-kHz häälitsusi väherõõmustavatel rottidel

Mällo *et al.*, *Neuroscience* 2009, 164: 963-974; Raudkivi *et al.*, *Acta Neuropsychiatrica* 2012, 24: 208-214

# Extracellular 5-HT levels higher in LC rats after chronic variable stress

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Raudkivi *et al.*, *Acta Neuropsychiatrica*, 2012, 24: 208-214

# Amino acids: Chronic stress effect, or function of positive affect?

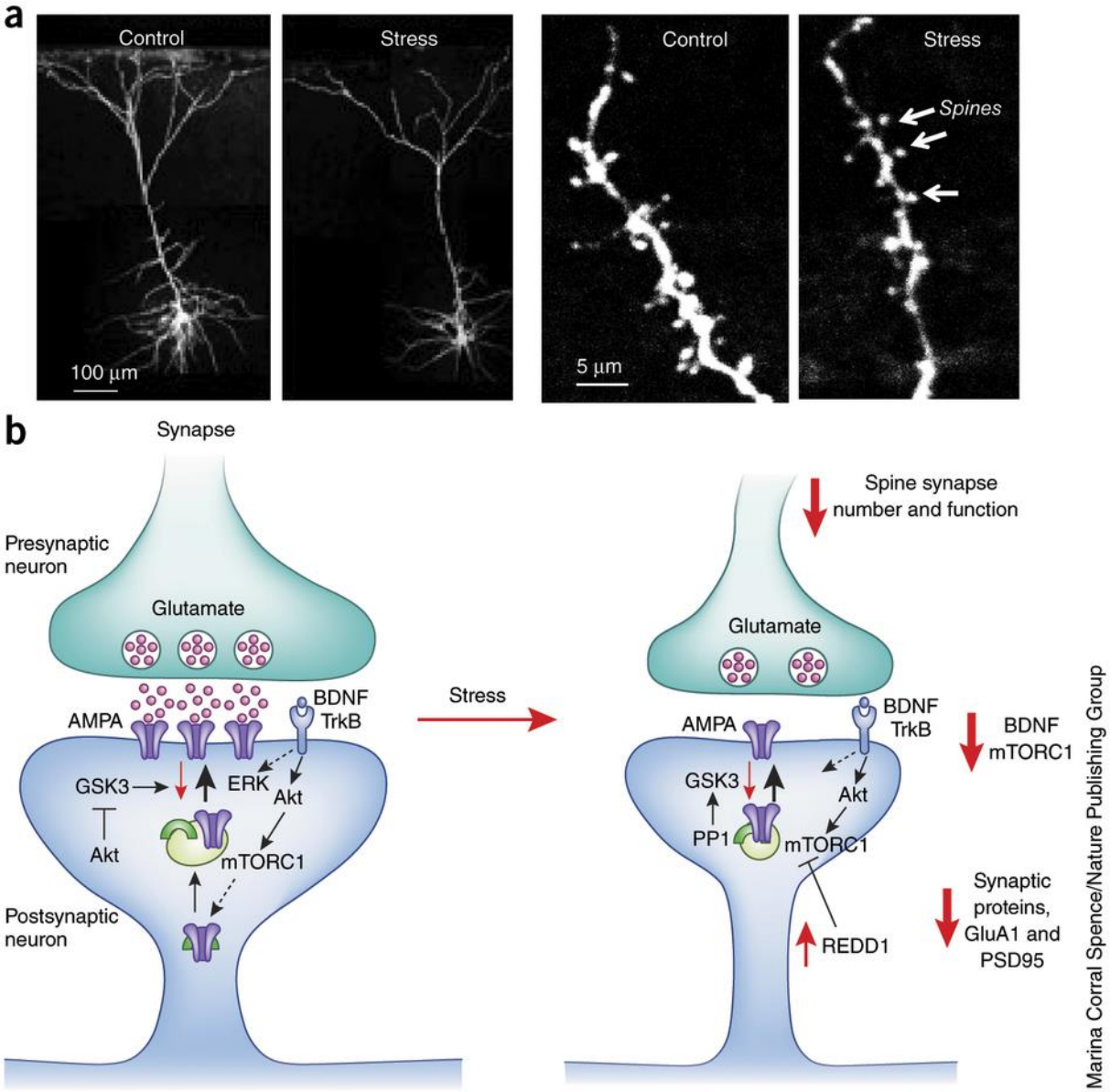
| | HC-control | HC-stress | LC-control | LC-stress |
|---|---|---|---|---|
| ß-alanine | 5.1 ± 0.6 | 4.7 ± 0.3 | 4.8 ± 0.6 | 3.3 ± 0.5 |
| isoleucine * | 12.0 ± 0.6 | 12.2 ± 1.0 | 10.3 ± 0.7 | 10.1 ± 0.7 |
| N-acetylaspartic acid | 480.1 ± 21.8 | 480.4 ± 18.1 | 453.0 ± 25.5 | 475.7 ± 29.7 |

Mean (SEM); pmol/mg wet weight tissue
* LC/HC ANOVA main effect $F(1,34)=5.3$; $p<0.05$

Kõiv *et al., European Neuropsychopharmacology* 2016, 26: 631-643

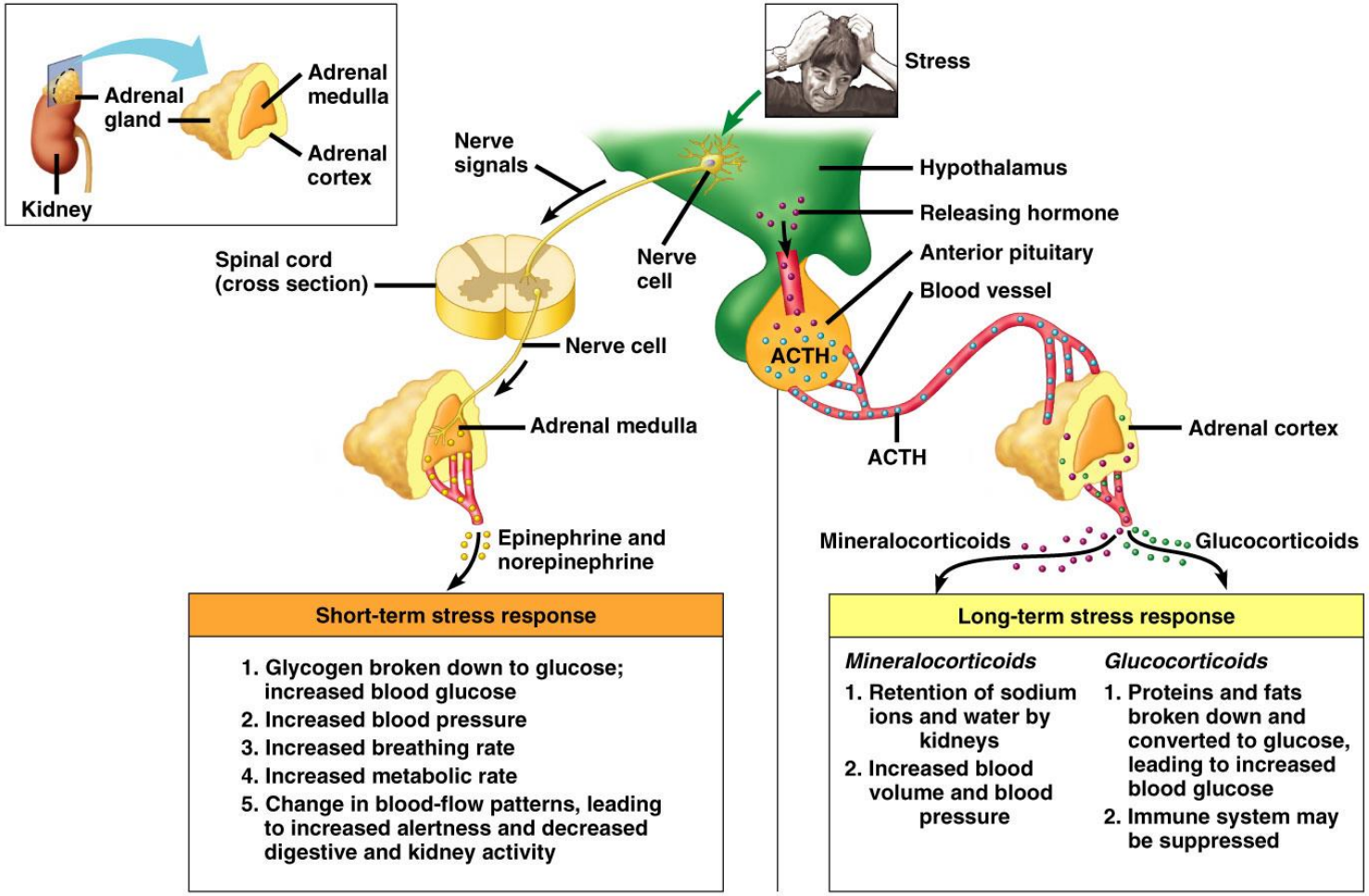
# Stress on halb

- Dendriitidel vähem hargnemisi ja ogasid
- Vähem ajustpärineva närvikasvufaktori mõju ja sünaptilisi valke




Duman *et al., Nature Medicine* 2016, 22: 238-249

# Stressiteljed ulatuvad kõikjale… ja stress pole tingimata paha

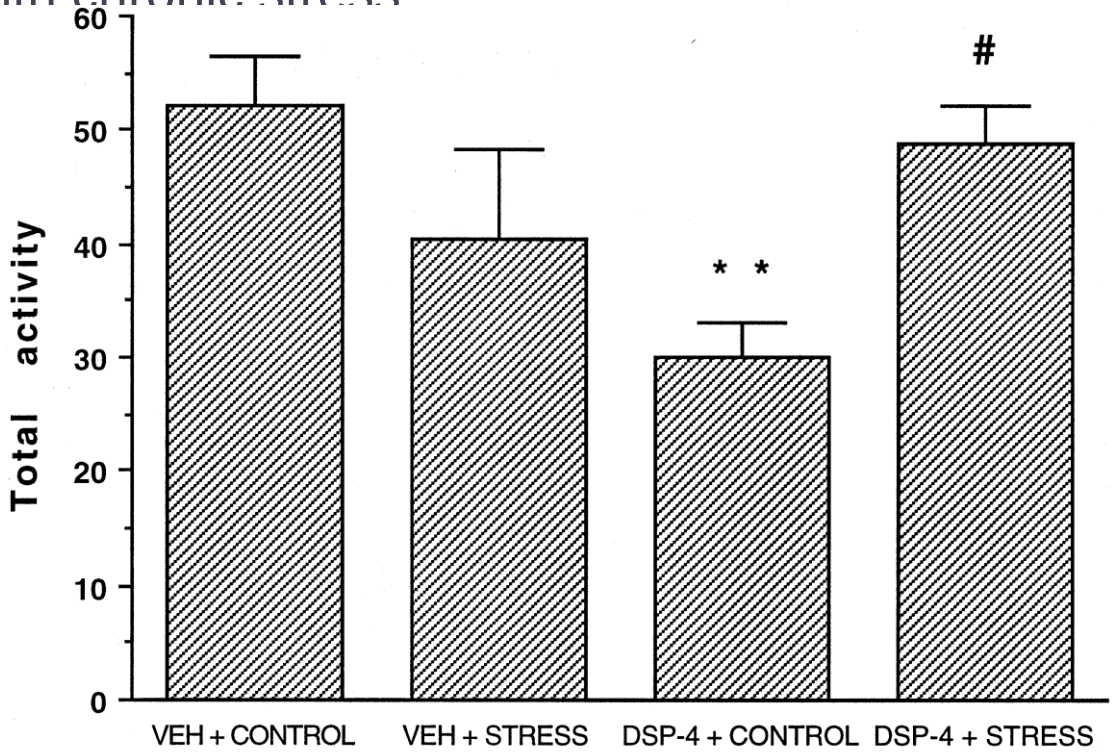





http://www.austincc.edu/apreview/PhysText/Endocrine.html

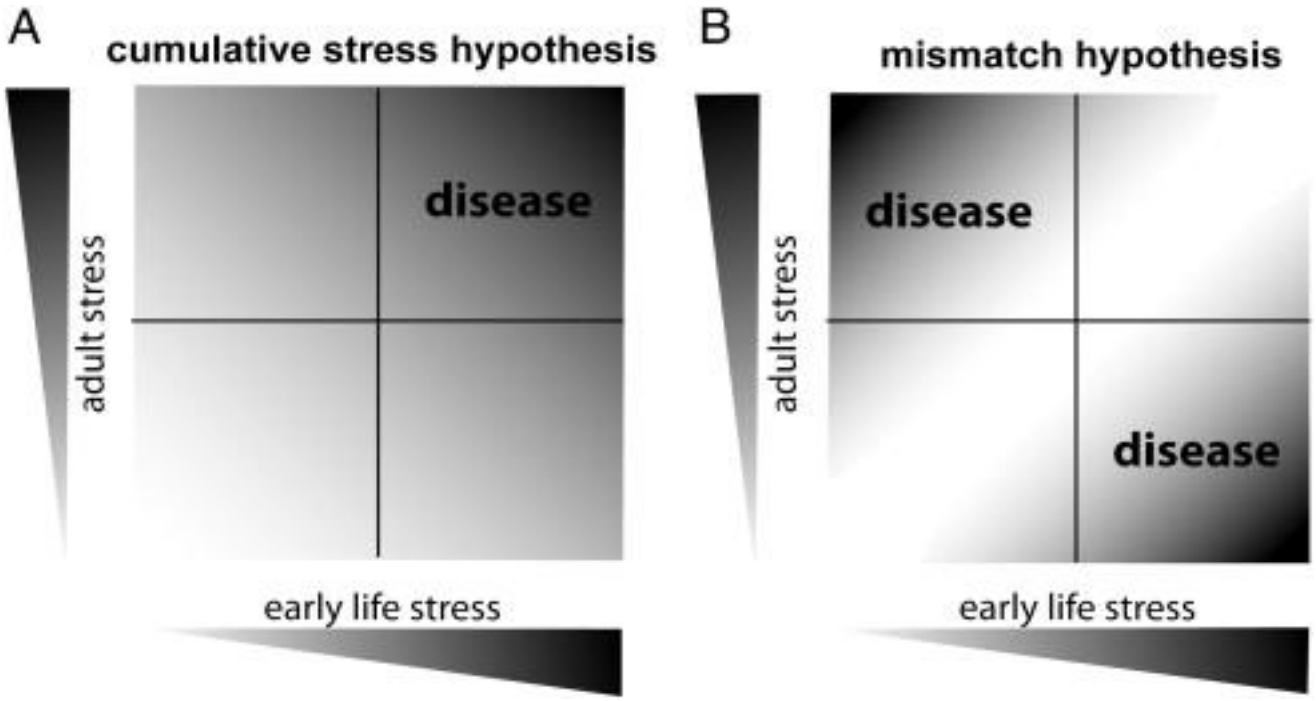
# Dull life is bad. Mild stress is good. Especially if your mind (read: LC) is peaceful ☺

Activity in a novel environment after DSP-4 (50 mg/kg) pretreatment: interaction with chronic stress



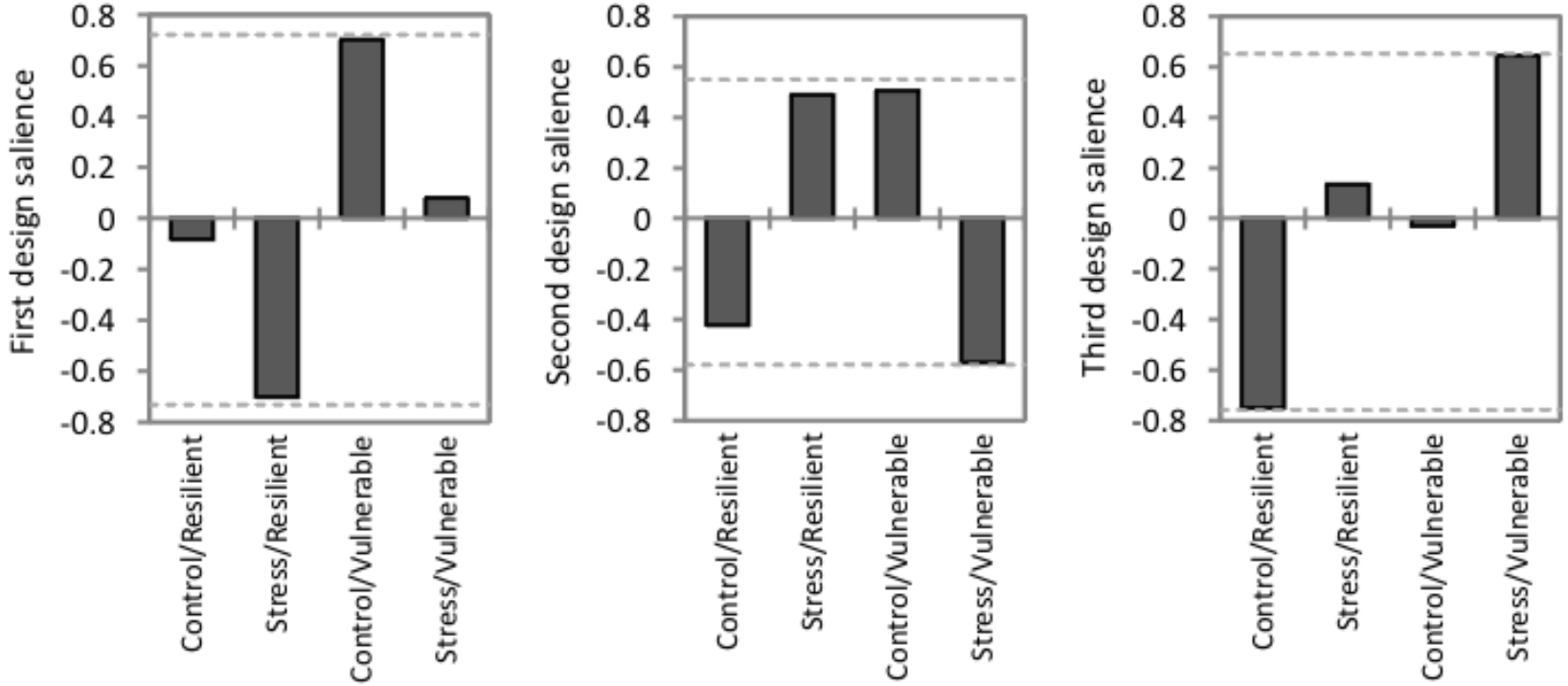

Harro *et al., Eur. Neuropsychopharmacol.* 1999, 10: 5-16

# Kumulatiivne stress või ootamatu stress?




Nederhof and Schmidt, *Physiology & Behavior* 2012; 106, 691-700

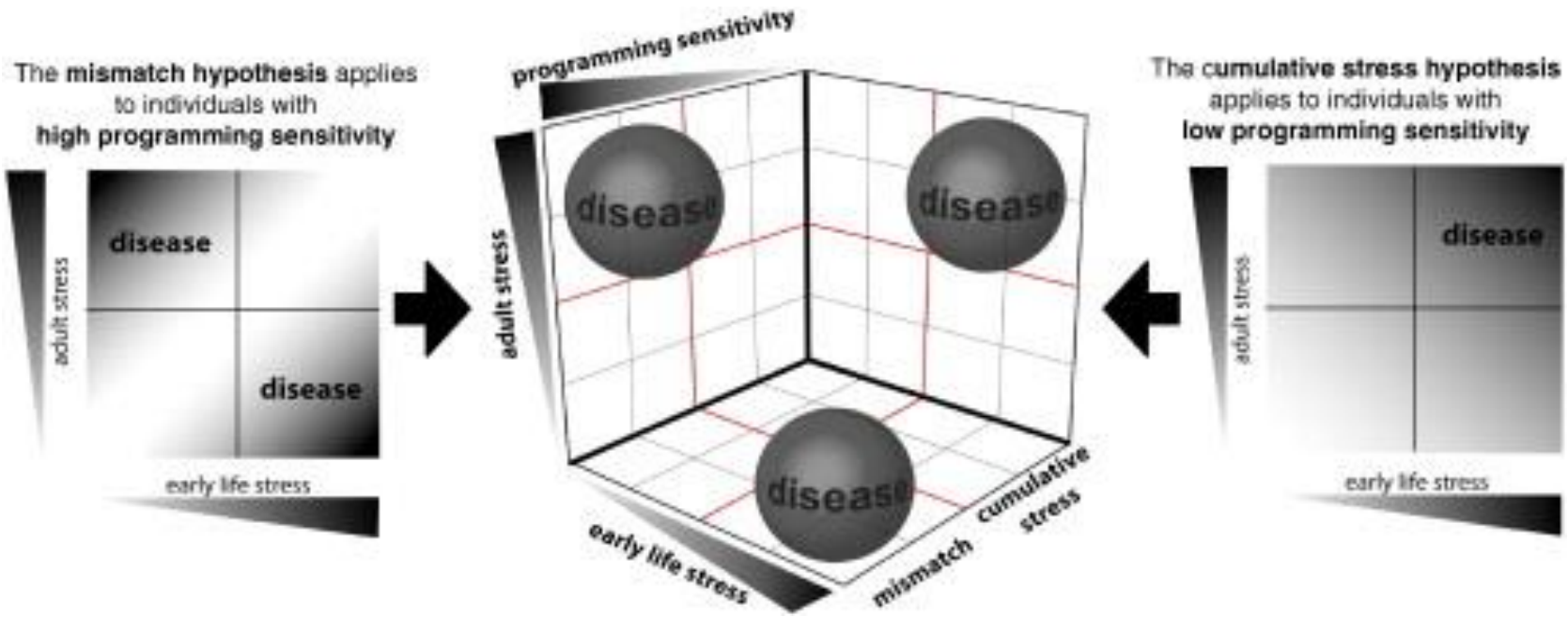
# Mis *keskkonnas* juhtub?




Regional COX activity across vulnerability and chronic stress experiments: one vulnerability, three stress responses

Harro *et al., Behavioural Brain Research* 2014, 267: 83-94

# Inimesed on erinevad, alates geenidest ja lapsepõlvest

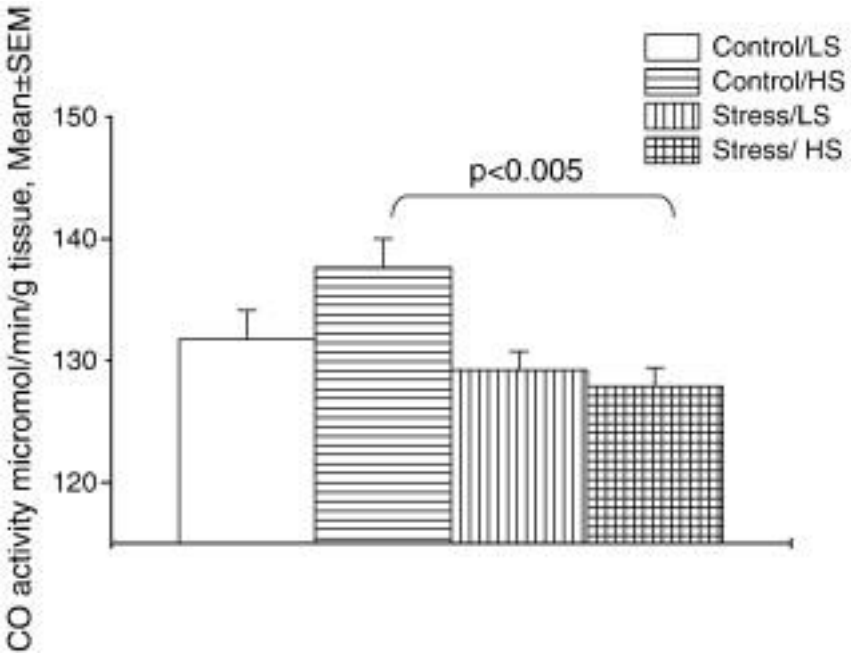



Nederhof & Schmidt, *Physiology & Behavior* 2012; 106, 691-700

HOPE FOR DEPRESSION
RESEARCH FOUNDATION

# Kes maiustama harjunud, selle aju on kurjale tundlikum?

High levels of sucrose consumption: behavioural and neurochemical sensitivity to stress




Kanarik *et al.*, *European Neuropsychopharmacology* 2011, 21: 92-107

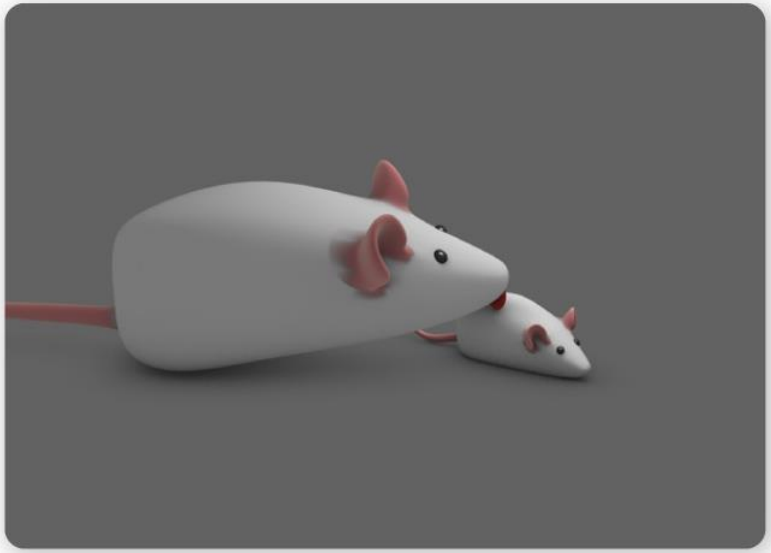
# A remark on general vulnerability: ADHD and prevalence of several diseases in Swedish registries

| | With ADHD | Without ADHD | |
|---|---|---|---|
| **Comorbidity** | **Prevalence (95% CI), %** | **Prevalence (95% CI), %** | **PR (95% CI)** |
| **Substance use disorder** | 35.1 (34.7 - 35.5) | 3.6 (3.6 - 3.6) | 9.7 (9.6 - 9.9) |
| **Depression** | 42.3 (41.9 - 42.7) | 4.7 (4.7 - 4.7) | 9.0 (8.9 - 9.1) |
| **Bipolar disorder** | 14.3 (14.0 - 14.6) | 0.7 (0.7 - 0.7) | 20.0 (19.5 - 20.4) |
| **Anxiety** | 44.7 (44.3 - 45.0) | 4.9 (4.9 - 4.9) | 9.1 (9.0 - 9.2) |
| **Obesity** | 6.8 (6.6 - 7.0) | 2.2 (2.2 - 2.2) | 3.0 (2.9 - 3.1) |
| **Type 2 diabetes mellitus** | 3.9 (3.7 - 4.1) | 1.6 (1.6 - 1.6) | 2.4 (2.3 - 2.5) |
| **Hypertension** | 8.5 (8.2 - 8.8) | 4.5 (4.5 - 4.5) | 1.9 (1.8 - 2.0) |

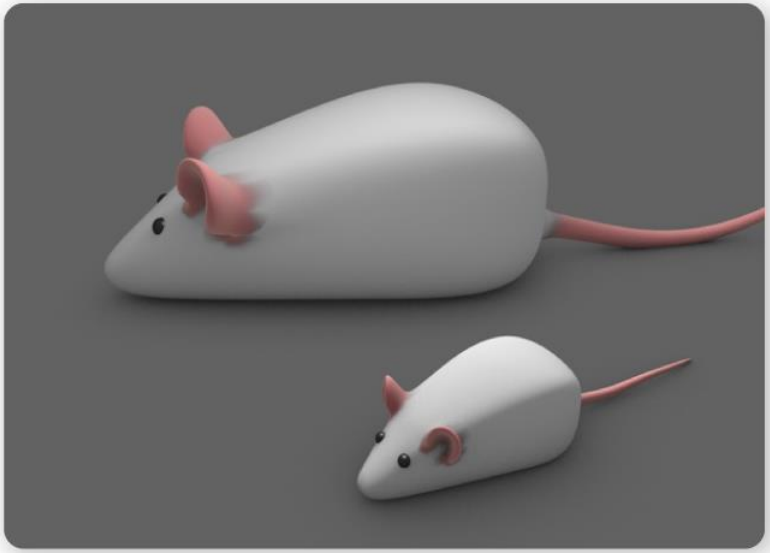
Chen *et al.*, *PLoS One* 2018; 13, e0204516

CoCA ADHD COMORBIDITY

# Maternal care affects the epigenome



Highly nurtured rat pups tend to grow up to be calm adults.



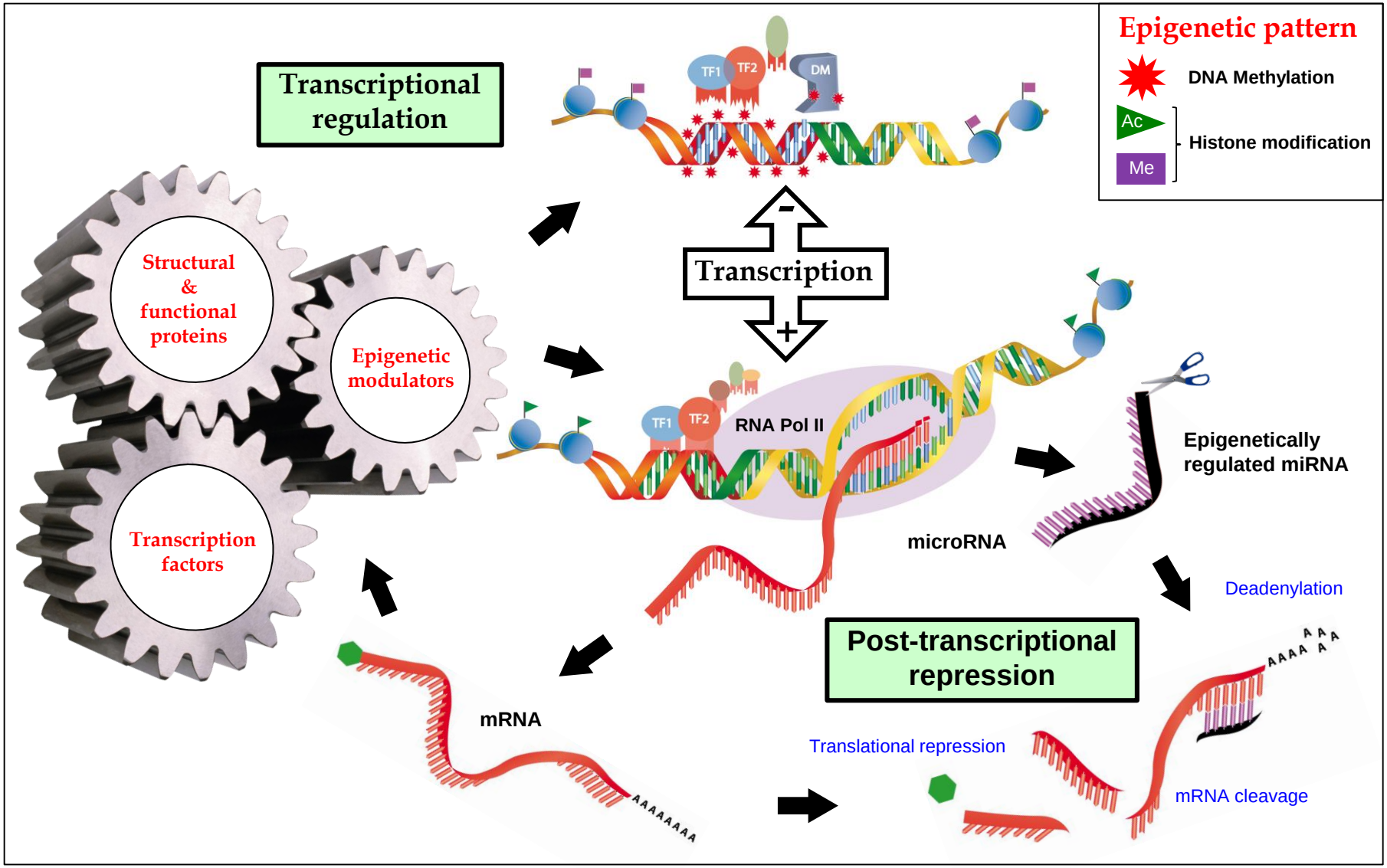
Rat pups who receive little nurturing tend to grow up to be anxious adults.

*Beyond genetics:* Epigeneetika ehk üks võimalik keskkonna püsimajääv mõju geeniekspressioonile

National Human Genome Research Institute

(Wever et al, 2004. Nature Neuroscience, 7, 847)

# Regulation: Epigenetic Mechanisms in the Regulation of Gene Expression




Courtesy Klaus-Peter Lesch

# Depressioonimoraal?

Aju on tervik suurte kohanemisvarudega, kuid vahel need ütlevad üles, tekib kaos … ja seejärel uus meta-stabiilne seisund

# ”The Depressed Brain”

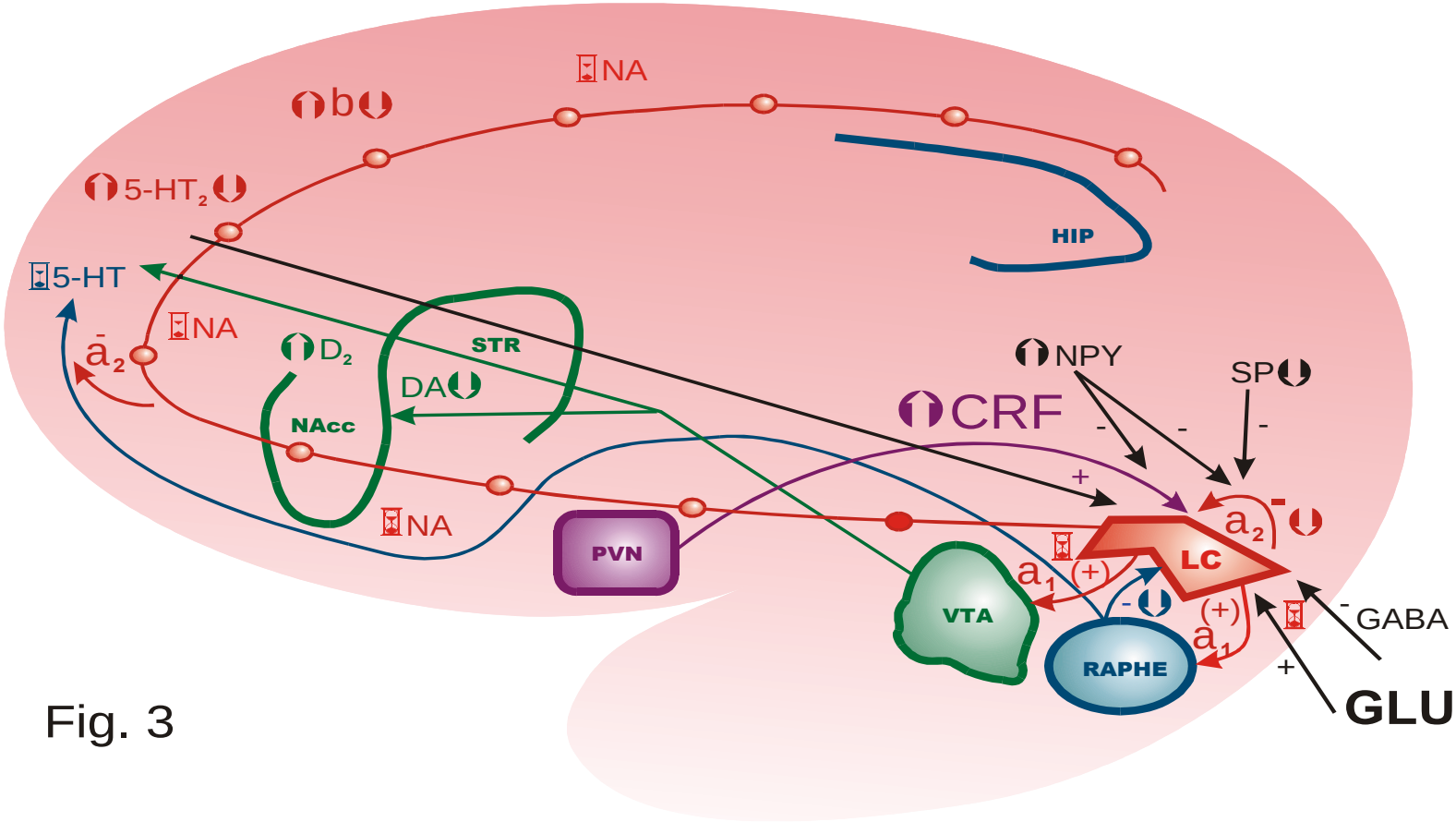
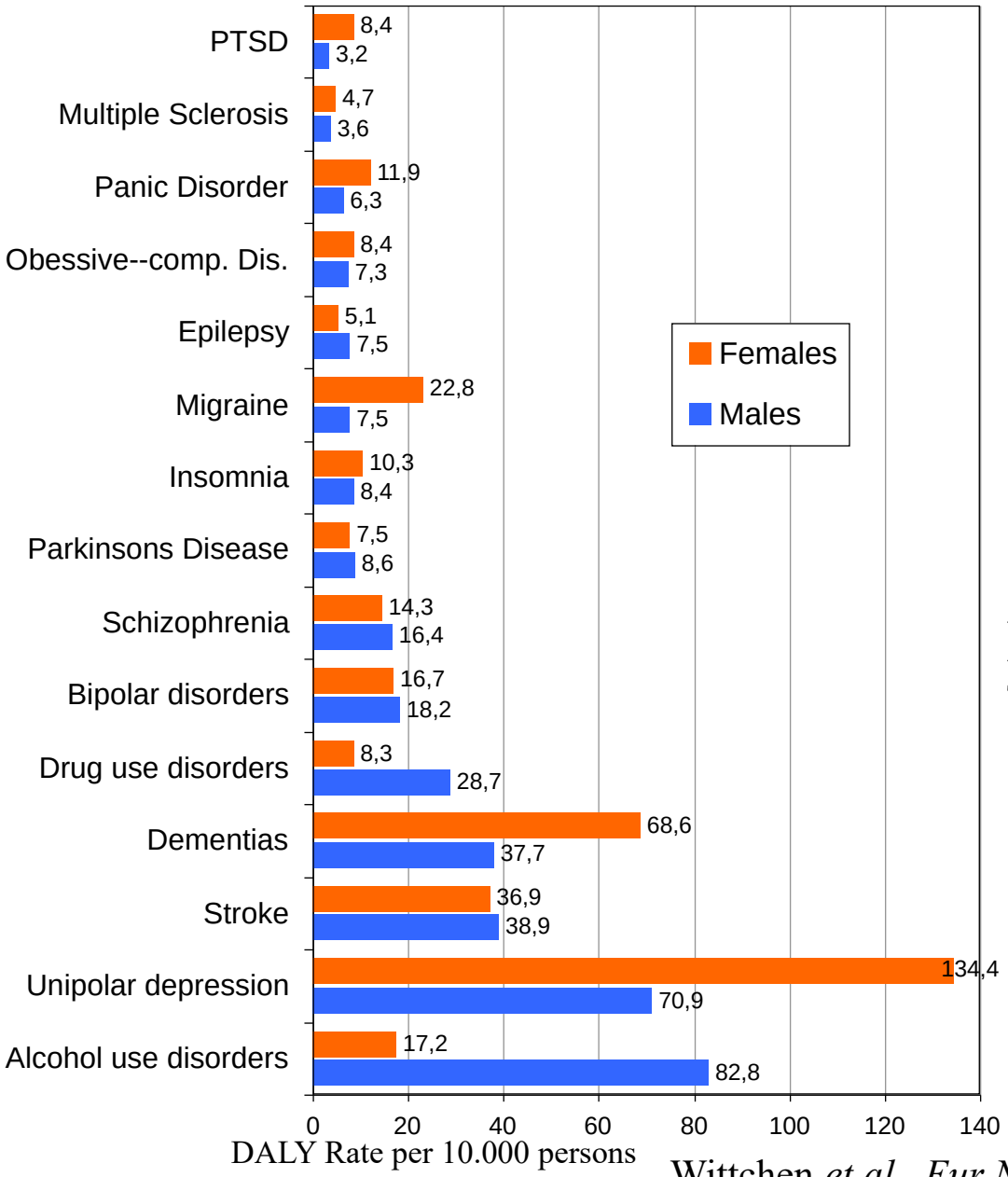



Fig. 3

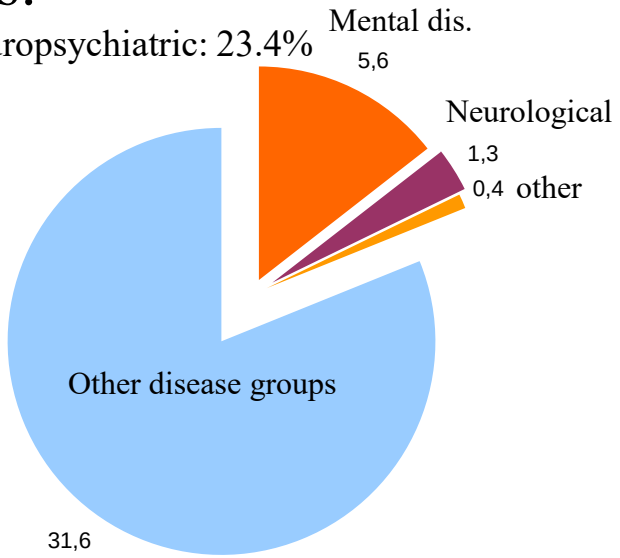
Harro & Oreland, *Brain Res Rev* 2001, 38: 79-128

# Revised 2011 DALY estimates: Gender comparison



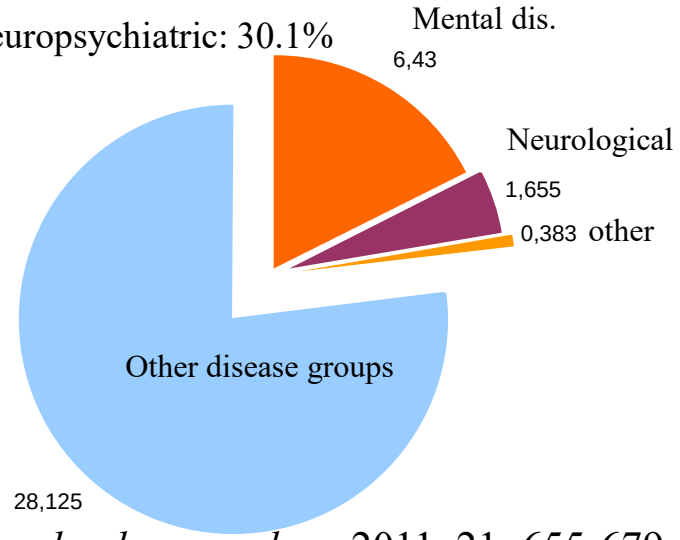

## Males:

Total neuropsychiatric: 23.4%




## Females:

Total neuropsychiatric: 30.1%




Wittchen *et al., Eur Neuropsychopharmacology* 2011, 21: 655-679

## Prevalence of psychiatric disorders in the ECPBHS

| | Affective | Anxiety | All disorders |
|---|---|---|---|
| **Younger birth cohort** | | | |
| Females (234) | 73 (31%) | 60 (26%) | 118 (50%) |
| Males (190) | 47 (25%) | 23 (12%) | 113 (60%) |
| All (424) | 120 (28%) | 83 (20%) | 231 (55%) |
| **Older birth cohort** | | | |
| Females (280) | 83 (30%) | 58 (21%) | 119 (42%) |
| Males (221) | 30 (14%) | 26 (12%) | 99 (45%) |
| All (510) | 113 (23%) | 84 (17%) | 218 (43%) |
| **Parents** | | | |
| Females (825) | 334 (40%) | 167 (20%) | 401 (49%) |
| Males (574) | 154 (27%) | 66 (12%) | 341 (59%) |
| All (1399) | 488 (35%) | 233 (17%) | 742 (53%) |

MINI

2014

2008

2011

Ajad on meestele rasked?

# Affective and anxiety disorders in mothers and fathers of the ECPBHS target group

| Disorder | Mothers YC | Mothers OC | Fathers YC | Fathers OC |
|---|---|---|---|---|
| Affective | 40.6% | 41.0% | 26.2% | 26.4% |
| Anxiety | 20.6% | 20.0% | 10.5% | 11.7% |

Geenid ei muutu nii ruttu.

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

CHAPTER

c0002

2

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

*Jaanus Harro and Mariliis Vaht*

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

Forthcoming in Victor R. Preedy (Ed.), *Neuroscience of Alcohol: Mechanisms and Treatment*. Elsevier 2019

# ”The Treatment-Refractory Brain”

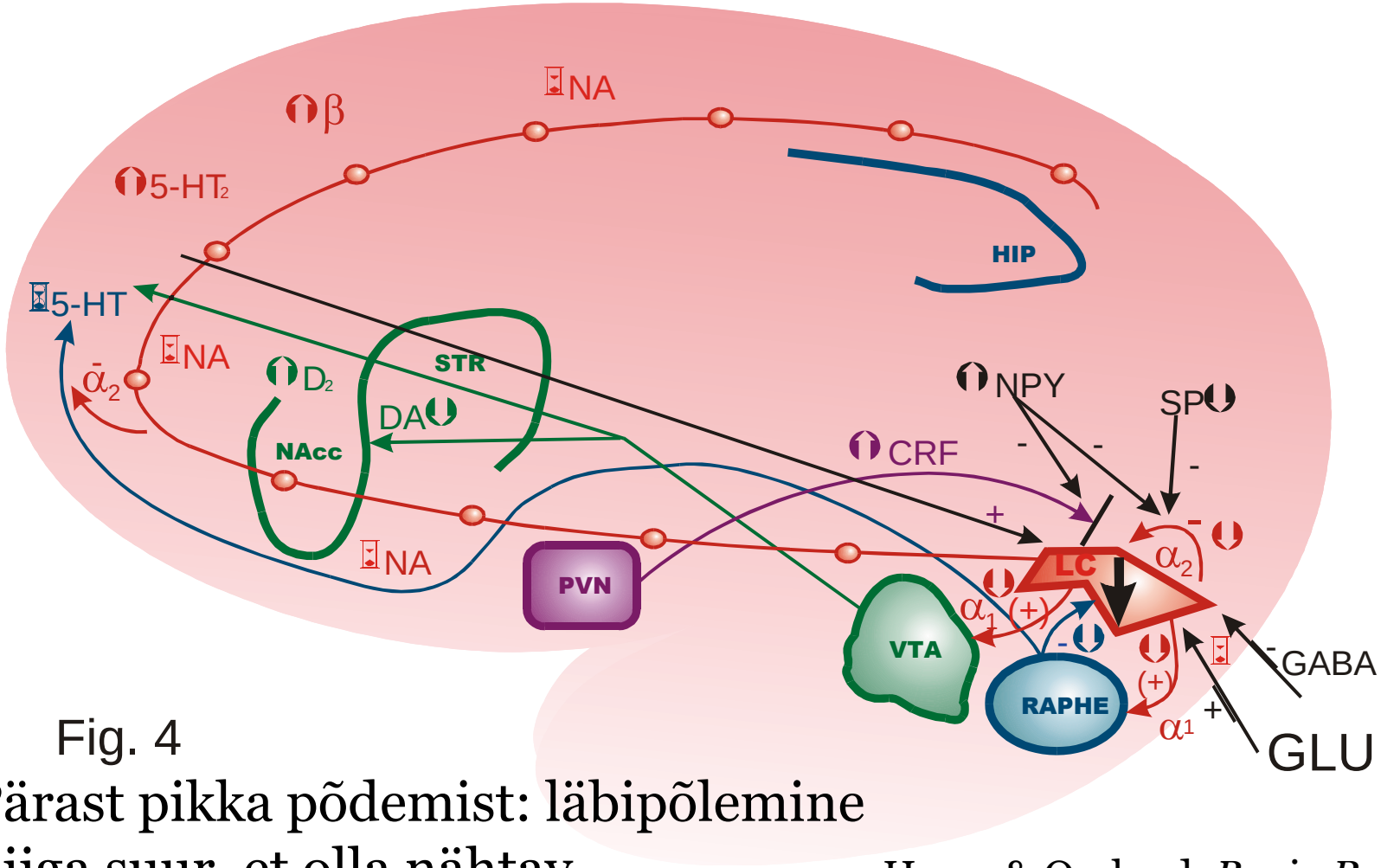


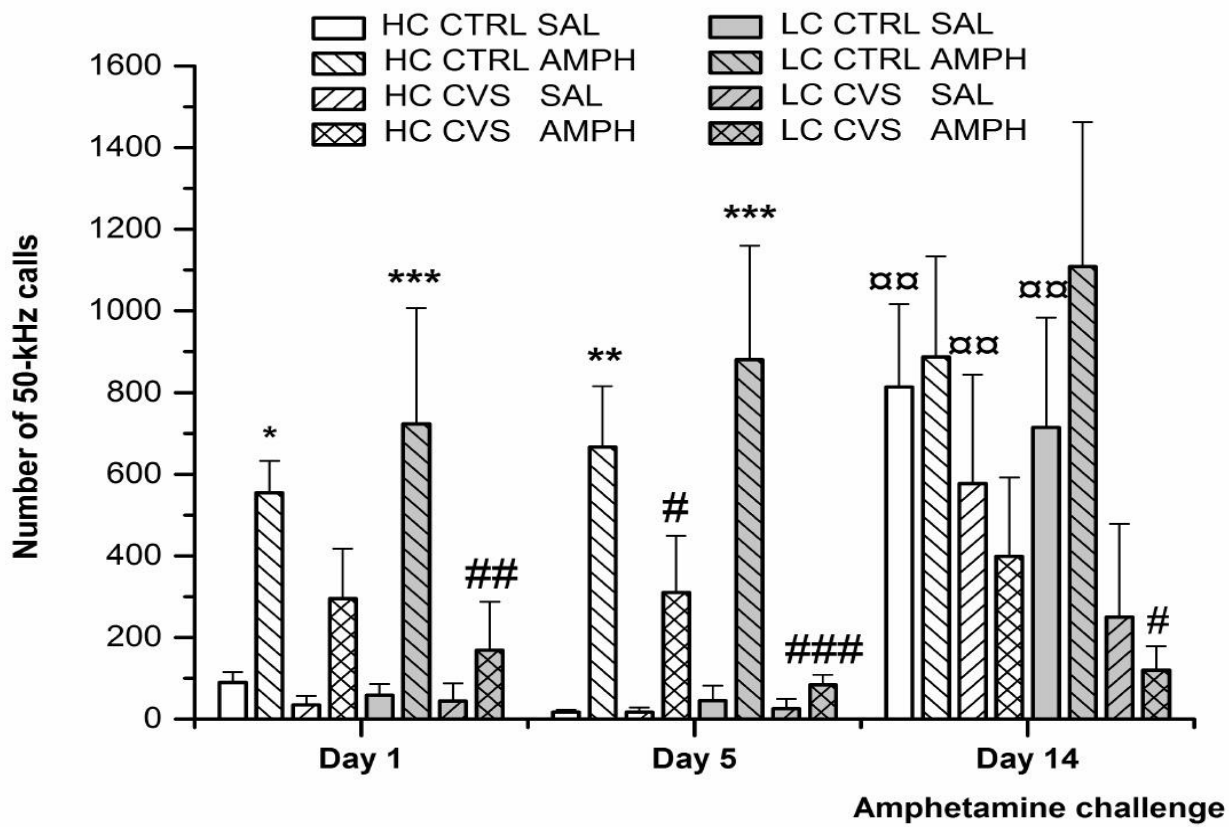

Fig. 4

Pärast pikka põdemist: läbipõlemine

Liiga suur, et olla nähtav

Harro & Oreland, *Brain Res Rev* 2001, 38: 79-128

# Rõõmutuid pika distressi peale isegi amfetamiin enam ei aita

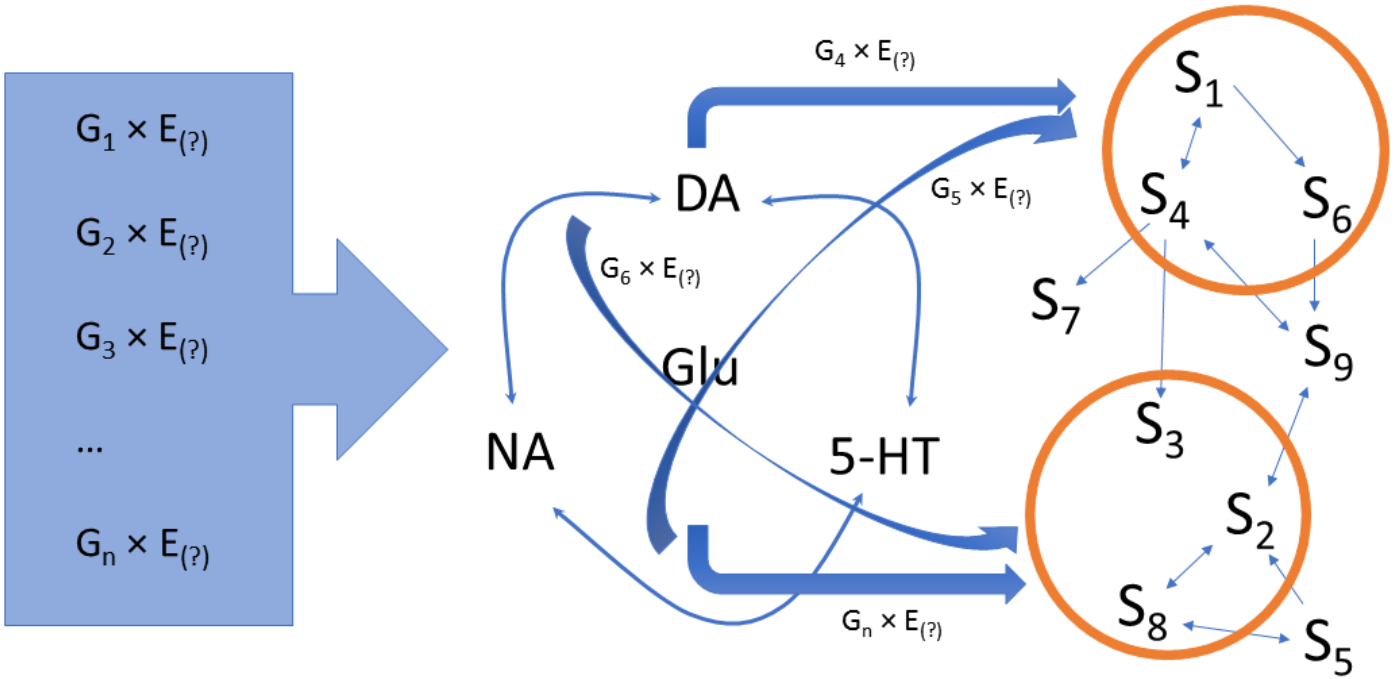



Kõiv *et al., European Neuropsychopharmacology* 2016, 26: 631-643

The third caveat was already voiced by K. Jaspers one century ago: “the method of living mosaic – i.e., the idea that disease entities are mosaic-like structures composed from a variety of individual and identical pieces – turns psychopathological investigation and diagnosis into something mechanical and petrifies discovery”1. In other terms, whether it is really possible to decompose currently identified mental disorders into “pieces” (variables or dimensions), which recur exactly with the same characteristics and presumably with the same neurobiological correlates in all those disorders, remains to be proved. A given symptom may instead have a different meaning and different underlying pathogenetic processes depending on the overall psychopathological context within which it emerges.

Mario Maj, *World Psychiatry* 2016, 15 (3) 193-194

# Missugune G × E on häire kujunemisel oluline?




Harro, *Cell and Tissue Research*, resubmitted

# Kokkuvõtteks?

- Alustage arenguspiraali hästi
- Ja tegelge sellega iganädalaselt
- Arvestades muutuvat keskkonda
- Kuid jäädes kindlaks sihile kauge tähe poole

Masaccio “Madonna and Child” (*Madonna del solletico*) *circa* 1426 (Uffizi, Firenze)