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Gene variants affecting cortico-amygdalar activity, and real life:
insights from the Estonian Children Personality Behaviour and Health Study

Jaanus Harro, MD, PhD

“Organization ... across the life span”, St-Petersburg State University,
 September 18, 2012

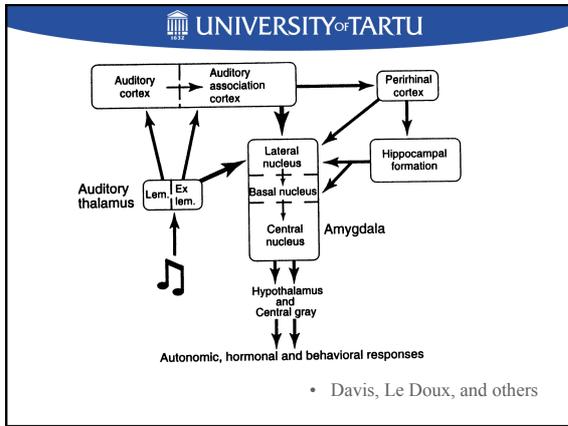


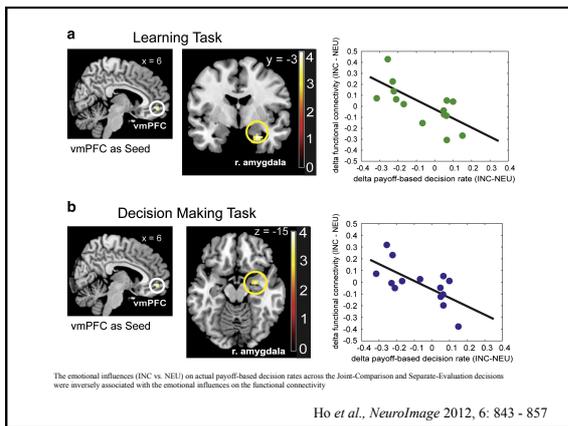
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amygdala, emotion control, mental health

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A schematic diagram for the involvement of midbrain structures in fear based on the model proposed by Fanselow [1991].





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the framework: ECPBHS

Why ECPBHS

- WHO: Health is a state of complete physical, mental and social well-being
- Determinants and indicators of health thus manifold
- Health determinants interact in a dynamic manner
- Lifestyle is the most important contributor to health
- Health (and other) effects are - or are not - often attributed to specific factors due to sample bias
- Estimation of effect size makes sense only while using population representative samples
- Causal inferences can only be made using longitudinal data
- Many determinants have early action that becomes persistent





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, 80% of the original sample recruited
- Longitudinal (*next slide*)
- Multidisciplinary
- Multi (birth) cohort
- Family aggregation
- Estimation of effect size for population



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EYHS sample Parents

1998/99 2001 2004 2007 2008 2011/12 2014

9-y (583) → 15-y (483) → 18-y (457) -----> 25-y

15-y (593) → 18-y (417+ 62) -----> 25-y (541)

IDEFICS sample

2007/08 2009/10 2013/14 2015/16

3-y (910) → 5-y (780) -----> 9-y

7-y (930) → 9-y (810) -----> 15-y

Estonian Children Personality Behaviour and Health Study

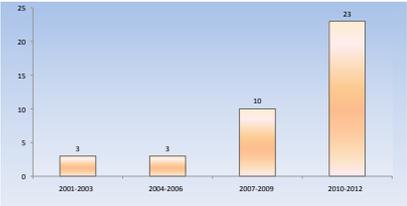
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ECPBHS data: general

- Personality (self and proxy assessment)
- Cognitive function (Raven; speed-accuracy tradeoff, stop signal, WCST, discrimination tests)
- Mood and impulsivity
- Health-related behaviour (questionnaires, accelerometry)
- Anthropometric and physiological measures
- Diet diary and interview
- Medical history: symptoms and diseases
- Clinical biochemistry
- DNA
- Socio-economic conditions of the family
- Relationships between family members
- Work stress and structured psychiatric interview
- **Parents: almost all this**

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ECPBHS productivity: 6 PhD degrees awarded, 11 PhD students



Period	Number of Papers
2001-2003	3
2004-2006	3
2007-2009	10
2010-2011	23

Figure 1. Number of *Web of Science* indexed full papers based on ECPBHS findings.

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**functional gene variants as proxy measures
for CNS activity: the 5-HTTLPR**

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**5-HTT binding potential and antidepressant
treatment response**

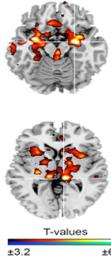
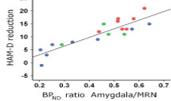
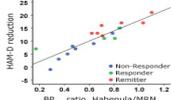




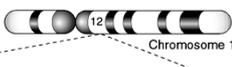
Fig 12 Significant associations between pretreatment SERT binding ratios in amygdala and habenula and treatment response. T-values are given in the color table (z-score = 1.64 = 5% rate). Statistical parameters map (SPM) showing highest...

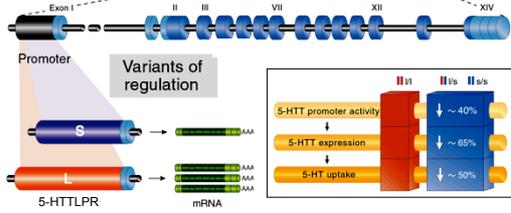
Lanzenberger *et al.*, *NeuroImage* 2012, 63: 874 - 881

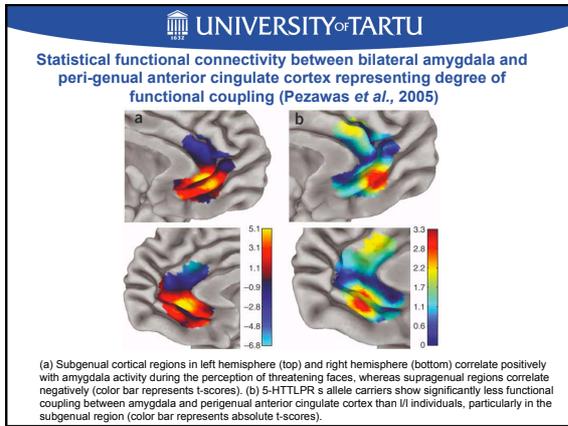
**Variants of the Serotonin Transporter Gene:
an Excellent Tool for Endophenotype Discovery**

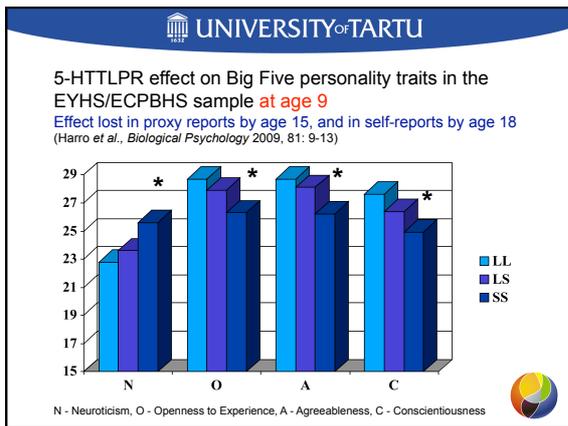
Lesch *et al.*, *Science* 1996

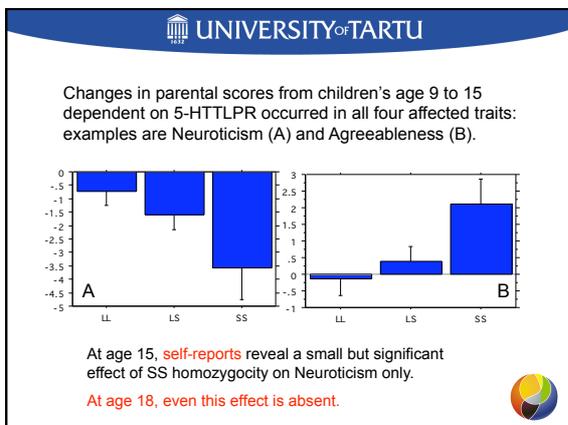
Genotype	Frequency
l/l	32 %
l/s	49 %
s/s	19 %

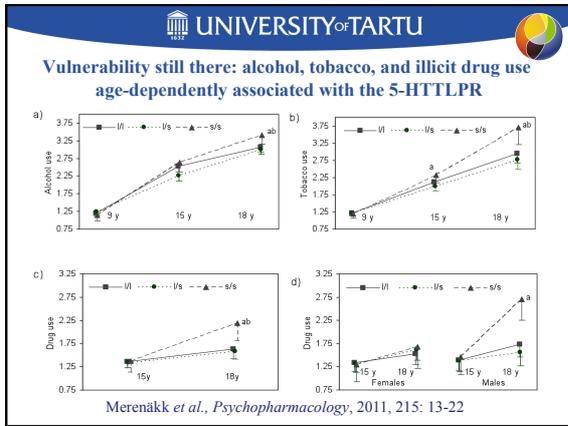


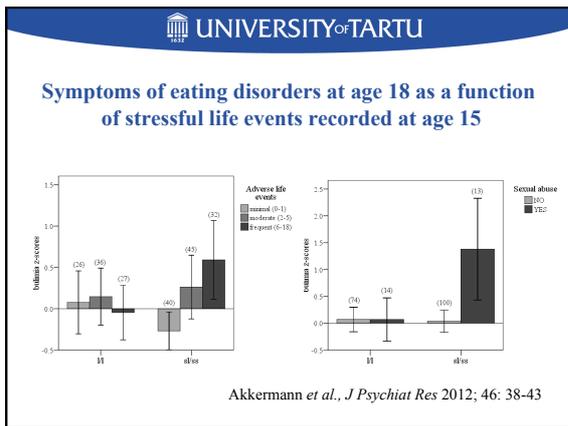


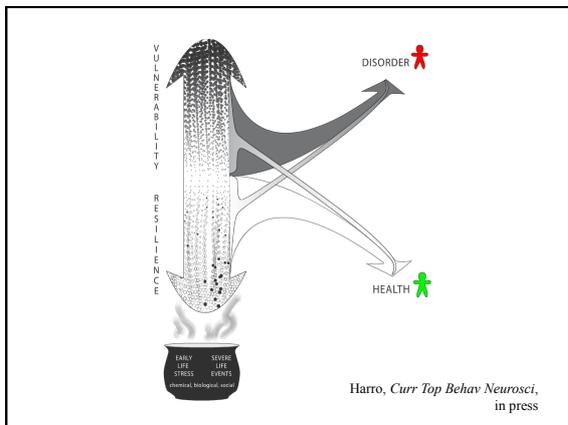














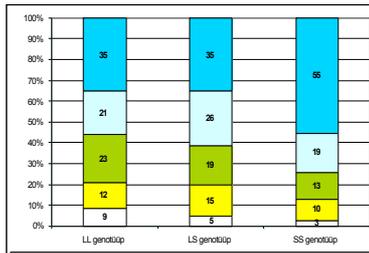
5-HTTLPR genotype and lifetime prevalence of anxiety disorders by age 25

5-HTTLPR genotype	ll-genotype	s-allele carriers	total
Males	n=92	n=130	n=222
Anxiety disorder	10	16	26
No	82	114	196
Females*	n=106	n=172	n=278
Anxiety disorder	29	29	58
No	77	143	220

* $\chi^2=4.38$; $p=0.036$

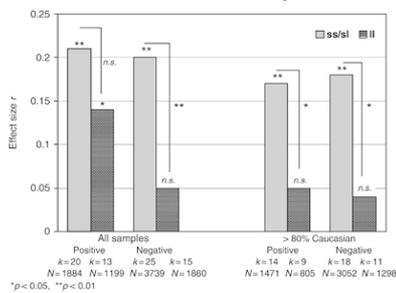


How to cope with predisposition to neuroticism: continue education (while residing in a region with strong educational traditions)

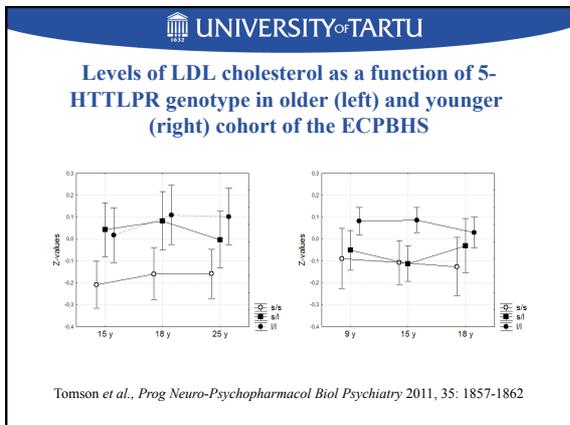


Educational achievements by age 25. Blue: university degree obtained.

5-HTTLPR s-allele carriers more malleable, at least in cultures dominated by Caucasians

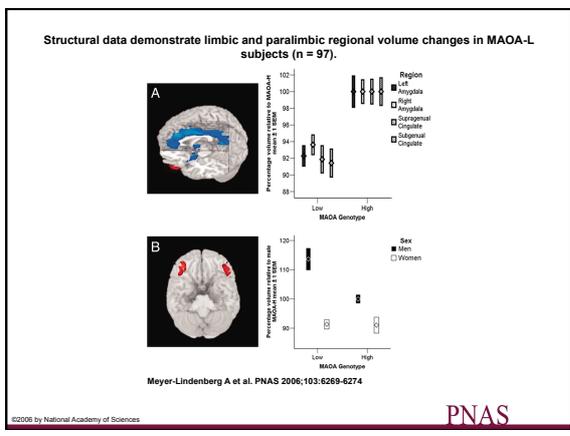


Ijzendoorn et al., *Transl Psychiatry* 2012, 2:e147

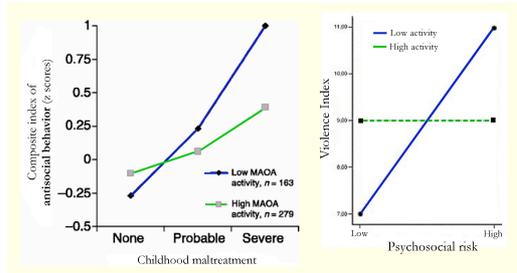


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MAOA, the “aggressiveness gene”



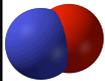
MAO-A genotype interaction with environment and risk for antisocial behaviour among boys



Caspi A., et al., Science (2002) Nilsson KW, et al., Biol Psychiat (2006)

But evidence that MAOA-L alleles helpful in financial decision-making under risk (Frydman et al., Proc Biol Sci 2011, 278: 2053-2059)

NOS1



Nitric oxide as a messenger

- 1980 Furchgott and Zawadzki observed blood vessel relaxation after stimulation of endothelium
- Moncada identified this endothelium-derived relaxing factor as NO
- NO is a mediator in the nervous system and in cardiovascular, renal, pulmonary, endocrine, and immune systems
- Synthesized by NO synthase: constitutive and inducible
- Neuronal NOS (also NOS-I) is expressed in neurons and is activated by glutamate via NMDA receptors

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NOS1 Ex1f VNTR s/s genotype increases functional impulsivity (Laas et al., *Psychopharmacology* 2010, 209: 255-261; Reif et al., *Psychopharmacology*, in press), but ...

... with inferior family relationship also promotes dysfunctional impulsivity

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Thus, NOS1 Ex1f VNTR s/s genotype increases dysfunctional impulsivity with inferior family relationships, but ...

... multiple severe adverse life events enhance dysfunctional impulsivity in subjects with l/l genotype

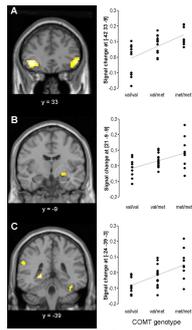
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Katehhoool-o-metüültransferaas (COMT)

- COMT on katehhooolamiine (noradrenaliin, adrenaliin ja dopamiin) lammutav ensüüm
- COMT neljandas eksonis üks SNP põhjustab aminohappevahetuse ensüümis (valiin vs metioniin): Val158Met polümorfism
- Val/Val genotüübil kõrgem COMT aktiivsus ja 3-4-korda madalam dopamiini tase kui Met/Met genotüübil
- COMT aktiivsus on eriti tähtis DA-talitlusele prefrontaalses ajukoores
- Met-alleeli kandjatel on suurem prefrontaalne ajuaktiivsus, parem töömälu ja täpsemad otsustusprotsessid, kuid Met/Met genotüüp on emotsionaalselt labiilsem

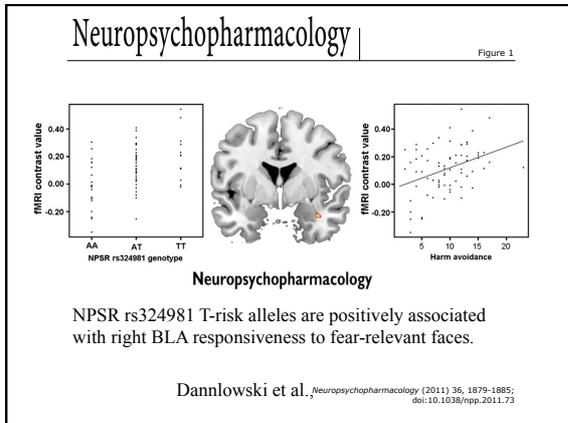
COMT

Correlation between COMT met158 allele dosage (0 = val/val, 1 = val/met, or 2 = met/met) and activation by unpleasant stimuli of the ventrolateral PFC (A), right amygdala (B), and left dorsal hippocampus (C).



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Smolka M N et al. J. Neurosci. 2005;25:836-842

NPSRI



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